Drug Class Review

Second Generation (Atypical) Antipsychotic Agents

28:16.08.04 Atypical Antipsychotics

Aripiprazole (Abilify®; others)
Asenapine (Saphris®)
Brexpiprazole (Rexulti®)
Cariprazine (Vraylar®)
Clozapine (Clozaril®; others)
Iloperidone (Fanapt®)
Lurasidone (Latuda®)
Olanzapine (Zyprexa®; others)
Paliperidone (Invega®)
Quetiapine (Seroquel®; others)
Risperidone (Risperdal®; others)
Ziprasidone (Geodon®)

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Executive Summary

Introduction: The antipsychotic agents have been used for over 6 decades to treat psychosis associated with schizophrenia, bipolar mania, acute agitation and other mental health conditions. All of the second-generation atypical antipsychotics are labeled for the treatment of schizophrenia and some are also labeled for use in the treatment of bipolar disorder, depression, autism and Tourette's disorder. All of the agents are available in oral tablet or capsule formulations and many of the agents are available in orally disintegrating tablets, oral solutions and injectable formulations which may be helpful to improve compliance or patient preference.

Clinical guidelines for the treatment of schizophrenia treatment with a single antipsychotic agent but do not recommend any of the agents over another. Treatment with more than one antipsychotic agent should be avoided and clozapine is recommended in treatment-resistant schizophrenia disease. Clinical guidelines for the treatment of bipolar disorder recommend medication therapy for acute mania episodes with mood stabilizers and select anticonvulsant or antipsychotic agents. Medication therapy should be continued until full remission is achieved and combination therapy is recommended in patients with continued treatment-resistance to a single agent. Clinical guidelines for the treatment of depression recommend use of a second-generation antidepressant for the treatment of depression; adjunctive treatment with another class of medications, including atypical antipsychotic agents, is recommended in patients who are treatment-resistant to antidepressant monotherapy.

Clinical Efficacy: Clinical experience with the second-generation atypical antipsychotic agents in treating patients with mental health disorders is extensive. The majority of comparative evidence evaluated in this report comes from the Oregon Report and 11 systematic review trials involving nearly 600 clinical trials and over 66,000 patients. Risperidone and olanzapine are included in most systematic reviews, meta-analyses and clinical trials evaluating the efficacy of the second-generation antipsychotic agents. Limited evidence is available for the new agents: brexpiprazole, cariprazine and iloperidone. In general, similar rates of efficacy were demonstrated across the available 12 second-generation antipsychotic agents in the treatment of schizophrenia, bipolar disorder and depressive disorder. Five patient populations may require special consideration when being treated with the second-generation atypical antipsychotic agents: geriatric patients, pediatric patients, patients with metabolic disease, patients with seizure disorders and patients with a drug and alcohol abuse disorder. In general, these patients may require changes in dosing schedules, reductions in duration of therapy, judicious medication selections and frequent follow-ups.

Adverse Drug Reactions: The most common adverse effects reported with the second-generation atypical antipsychotic agents include extrapyramidal symptoms, anticholinergic side effects, sedation, cardiovascular effects and metabolic effects. Serious adverse effects reported with the agents include neuroleptic malignant syndrome, seizures, agranulocytosis, venous thromboembolism, cardiovascular arrhythmias and suicidal behavior. Differences in adverse events between the second-generation atypical antipsychotic agents are reported in the literature and are not always consistent. Differences in adverse event rates may be tied to pharmacological actions; differences in binding affinity between the antipsychotic agents for each of the dopamine tracts may result in differences in adverse effects. Careful attention should be paid to

adverse effect profile for each individual agent when selecting an agent for treatment of mental health disorders.

Summary: Overall, the second-generation atypical antipsychotic agents are effective treatment options for mental health disorders. When compared in clinical trials, the agents demonstrate similar rates of efficacy with varying rates of adverse effects. The second-generation antipsychotic products are available in many dosage forms, varying potencies and differing durations of action. Treatment management must be individualized for each patient and include careful evaluation of patient history, age, comorbidities, type and severity of mental health disorder, underlying diseases and concurrent medications.

Introduction

The antipsychotic agents have been used for over 6 decades to treat psychosis associated with schizophrenia, bipolar mania, acute agitation and other mental health conditions.[1-3] As a class, the antipsychotic agents are divided into two main categories: first-generation agents and second-generation, or atypical, agents. The first-generation antipsychotic agents are characterized by an increased risk of movement disorders (extrapyramidal side effects and tardive dyskinesia) and typically include chlorpromazine, droperidol, flupentixol, fluphenazine, haloperidol, loxapine, methotrimeprazine, molindone, periciazine, perphenazine, pimozide, pipotiazine, prochlorperazine, thioridazine, thiothixene, trifluoperazine and zuclopenthixol.[1-6] Other than the difference in adverse effects, the first-generation and second-generation agents demonstrate similar characteristics including general mechanism of action and clinical efficacy.[7] The agents included in the second-generation antipsychotic category include aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone. This report will focus on the comparative clinical safety and efficacy evidence available for the second-generation agents.

All of the second-generation atypical antipsychotic agents are available in oral tablet or capsule formulations.[1,2] Five of the twelve available second-generation agents are available in orally disintegrating formations: aripiprazole, asenapine, clozapine, olanzapine and risperidone. Two of the second-generation agents are available in extended-release oral formulations: paliperidone and quetiapine. Four of the second-generation agents are available in extended-release intramuscular injection formulations: aripiprazole (every 4-6 weeks), olanzapine (every 2-4 weeks), paliperidone (every 1-3 months) and risperidone (every 2 weeks). Two of the second-generation agents are available in immediate-release intramuscular injection formulations: olanzapine and ziprasidone. Three of the second-generation agents are available in oral liquid formulations: aripiprazole (solution), clozapine (suspension) and risperidone (solution). Iloperidone is also available in an oral tablet titration pack. Currently, one second-generation antipsychotic combination product is available for use in the US: olanzapine/ fluoxetine.[1] For a summary of the available second-generation atypical antipsychotic agents, see Table 1. All of the atypical antipsychotics are labeled for the treatment of schizophrenia. Some of the agents are also labeled for use in the treatment of bipolar disorder, depression, autism and Tourette's disorder.[1] For a list of the second-generation atypical antipsychotic labeled indications, see Table 2.

Table 1. Comparison of the Second-Generation Atypical Antipsychotic Agents[1,2]

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Aripiprazole (Abilify; Abilify Discmelt [DSC]; Abilify Maintena) **Aripiprazole Lauroxil (Aristada)**	Intramuscular Suspension, reconstituted: Abilify Maintena 300 mg, 400 mg Oral Solution: 1 mg/mL (150 mL) Oral Tablet: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg Oral Tablet, dispersible: 10 mg, 15 mg Intramuscular, prefilled syringe: Aristada 441 mg, 662 mg, 882 mg	Oral Bipolar I disorder: Acute treatment of manic and mixed episodes associated with bipolar I disorder Irritability associated with autistic disorder: Treatment of irritability associated with autistic disorder Major depressive disorder: Adjunctive treatment of major depressive disorder Schizophrenia: Treatment of schizophrenia Tourette disorder: Treatment of Tourette disorder Injection Schizophrenia: Treatment of schizophrenia	Depression with psychotic features Psychosis/agitation related to Alzheimer disease and other dementias	Bipolar I disorder (acute manic or mixed episodes) Oral Monotherapy: 15-30 mg once daily Oral Adjunct (to lithium or valproic acid): 10-30 mg once daily Depression (adjunct to antidepressant) Oral: 2-15 mg/day Schizophrenia Oral: 10-30 mg once daily Intramuscular (Maintena): 400 mg once monthly (doses should be separated by ≥26 days) Intramuscular (Aristada): if oral dose is 10 mg/day = IM (Lauroxil) 441 mg/month; oral 15 mg/day = IM (Lauroxil) 662 mg/month; oral aripiprazole ≥20 mg/day = IM (Lauroxil) 882 mg every 4-6 weeks **Dosage adjustment recommended with concurrent strong CYP450 inducer/inhibitor (2D6, 3A4) therapy or based on CYP2D6 metabolizer status **IM Therapy: Establish tolerability with oral aripiprazole prior to initiating IM treatment; continue oral therapy for 14 days after first IM dose	Bipolar I disorder (acute manic or mixed episodes) Children ≥10 years and Adolescents: 10 mg once daily as monotherapy or as adjunct to lithium or valproic acid; maximum of 30 mg/day Autistic disorder (irritability) Children ≥6 years and Adolescents: 2-15 mg/day; periodically assess need for ongoing treatment Schizophrenia Adolescents ≥13 years: 10 mg once daily Tourette disorder Children ≥6 years and Adolescents: <50 kg- Initial: 2-10 mg/day ≥50 kg- Initial: 2-20 mg/day; periodically assess need for ongoing treatment	Intramuscular formulations - No All other formulations - Yes

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Asenapine (Saphris)	Sublingual Tablet, black cherry flavor: 2.5 mg, 5 mg, 10 mg	Bipolar disorder: Treatment of acute manic or mixed episodes associated with bipolar I disorder Schizophrenia: Treatment of schizophrenia	None listed	Bipolar disorder Monotherapy: 10 mg twice daily Adjunct (with lithium or valproate): 5-10 mg twice daily Schizophrenia 5-10 mg twice daily	Bipolar disorder Children ≥10 years and Adolescents: 2.5-10 mg twice daily; pediatric patients appear to be more sensitive to dystonia when dose is not slowly escalated	No
Brexpiprazole (Rexulti)	Oral Tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg	Major depressive disorder: Adjunctive treatment of major depressive disorder (MDD) Schizophrenia: Treatment of schizophrenia	None listed	Major Depressive disorder (adjunct to antidepressants) 0.5-3 mg once daily Schizophrenia 1-4 mg once daily **Dosage adjustment recommended with concurrent strong CYP450 inducer/inhibitor (2D6, 3A4) therapy or based on CYP2D6 metabolizer status	Not indicated	No
Cariprazine (Vraylar)	Oral Capsule: 1.5 mg, 3 mg, 4.5 mg, 6 mg Oral Capsule, therapy Pack: 1.5 mg (1) & 3 mg (6)	Bipolar I disorder: Acute treatment of manic or mixed episodes associated with bipolar I disorder Schizophrenia: Treatment of schizophrenia	None listed	Bipolar I disorder 3-6 mg once daily Schizophrenia 1.5-6 mg once daily ** Dosage adjustment with concurrent CYP450 inducer/inhibitor (3A4) therapy	Not indicated	No

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Clozapine (Clozaril; FazaClo; Versacloz)	Oral Suspension: Versacloz 50 mg/mL (100 mL) Oral Tablet: 25 mg, 50 mg, 100 mg, 200 mg Oral Tablet, Dispersible: 12.5 mg, 25 mg, 100 mg, 150 mg, 200 mg	Schizophrenia: Treatment of severely ill patients with schizophrenia who fail to respond adequately to antipsychotic treatment Suicidal behavior in schizophrenia or schizoaffective disorder: To reduce the risk of suicidal behavior	Bipolar disorder: treatment-resistant in adolescents/ adults Psychosis/agitation: treatment-resistant related to Alzheimer dementia Psychosis: treatment-resistant related to Lewy body disease Schizoaffective disorder	<u>Schizophrenia</u> 300-450 mg daily (in divided doses); max 900 mg/day <u>Suicidal behavior in schizophrenia or schizoaffective disorder</u> 300-450 mg daily (in divided doses); max 900 mg/day ** Prior to initiating treatment, obtain an absolute neutrophil count (ANC); ANC must be ≥1,500/ mm^3 to initiate treatment and monitored regularly	Not indicated	Suspension- No Tablets - Yes
Iloperidone (Fanapt; Fanapt Titration Pack)	Oral Tablet: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg Titration Pack: 1 mg (2s), 2 mg (2s), 4 mg (2s), and 6 mg (2s)	Schizophrenia: Treatment of adults with schizophrenia	None listed	6 - 12 mg twice daily; max 24 mg/day **Titrate to effect and to avoid orthostatic hypotension: start 1 mg twice daily with dosage adjustments not to exceed 2 mg twice daily (4 mg daily) every 24 hours; when reinitiating treatment after discontinuation (>3 days), follow titration schedule. ** Dosage adjustment with concurrent strong CYP450 inhibitors (2D6, 3A4)	Not indicated	No

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Lurasidone (Latuda)	Oral Tablet: 20 mg, 40 mg, 60 mg, 80 mg, 120 mg	Schizophrenia: Treatment of schizophrenia Bipolar disorder: Monotherapy or adjunctive therapy of depressive episodes associated with bipolar I disorder	None listed	Schizophrenia 40 mg once daily; max 160 mg daily Depressive episodes associated with bipolar I disorder (monotherapy or as an adjunct to lithium or valproic acid) 20 mg once daily; max 120 mg daily ** Dosing adjustment with concomitant CYP450 inhibitors/inducers (3A4)	Not indicated	No

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Olanzapine (Zyprexa; Zyprexa Relprevv; Zyprexa Zydis)	Intramuscular Solution, Reconstituted, short-acting: 10 mg Intramuscular Suspension, Reconstituted, long-acting: ZyPREXA Relprevv 210 mg, 300 mg, 405 mg Oral Tablet: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg Oral Tablet, Dispersible: 5 mg, 10 mg, 15 mg, 20 mg	Oral Schizophrenia: Treatment of the manifestations of schizophrenia Bipolar Disorder: Treatment of acute or mixed mania episodes associated with bipolar I disorder; maintenance treatment of bipolar I disorder; treatment-resistant or bipolar I depression Injection, extended-release (ER) (Zyprexa Relprevv): Schizophrenia: Treatment of schizophrenia Injection, immediate-release (solution): Agitation: Treatment of acute agitation associated with schizophrenia and bipolar I mania	Prevention of chemotherapy-associated delayed nausea or vomiting Delirium Delusional parasitosis Psychosis/agitation related to Alzheimer disease and other dementias Post-traumatic stress disorder Tourette syndrome	Schizophrenia Oral: 10 to 20 mg once daily; max 20 mg/day **start 5 mg and titrate by 5 mg daily at 1-week intervals Extended-release IM injection: 150 mg every 2 weeks or 300 mg every 4 weeks, max 300 mg/2 weeks or 405 mg/4 weeks **Establish tolerance to oral olanzapine prior to changing to IM injection. Patients established on oral olanzapine 10 mg daily = 150 mg every 2 weeks or 300 mg every 4 weeks; oral olanzapine 15 mg daily = 210 mg every 2 weeks or 405 mg every 4 weeks; oral olanzapine 20 mg daily = 300 mg every 2 weeks Bipolar I Monotherapy: Oral 5 - 20 mg daily; max 20 mg daily. Combination therapy (with lithium or valproate): Oral 5 - 20 mg daily Depression associated with bipolar disorder (in combination with fluoxetine): Oral 2.5 - 12.5 mg daily Agitation Short-acting IM injection: 5 -10 mg, 2 hours after the initial dose and 4 hours after the second dose is required to evaluate response, max 30 mg/day Depression (treatment-resistant, in combination with fluoxetine): Oral 2.5 - 20 mg daily	Bipolar I Adolescents ≥13 years: Oral 2.5 - 20 mg daily Depression associated with bipolar I disorder (in combination with fluoxetine): Children and Adolescents 10 to 17 years: Oral 2.5 mg - 12 mg daily Schizophrenia Adolescents ≥13 years: Oral 2.5 to 20 mg daily	Yes; except Intramuscular Relprevv injection

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Paliperidone (Invega; Invega Sustenna; Invega Trinza)	Intramuscular Suspension, as palmitate: Invega Sustenna 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL; Invega Trinza 273 mg/0.875 mL, 410 mg/1.315 mL, 273 mg/0.875 mL, 546 mg/1.75 mL, 819 mg/2.625 mL Oral Tablet, Extended Release: 1.5 mg, 3 mg, 6 mg, 9 mg	Schizophrenia: Treatment of schizophrenia Schizoaffective disorder (oral and monthly IM paliperidone): Treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants	Delusional parasitosis	<u>Schizoaffective disorder</u> Oral: 6 mg daily (range: 3-12 mg daily), max of 12 mg daily Intramuscular (Invega Sustenna): 78 to 234 mg every month <u>Schizophrenia</u> Oral: 6 mg daily (range: 3-12 mg daily), max of 12 mg daily Intramuscular (Invega Sustenna): 117 mg every month (range: 39 to 234 mg); Intramuscular (Invega Trinza): every 3 months, Sustenna dose 78 mg = 273 mg Trinza, Sustenna 117 mg = 410 mg Trinza, Sustenna 156 mg = 546 mg Trinza, 234 Sustenna = 819 mg Trinza **Prior to initiation, tolerability should be established with oral paliperidone or oral risperidone; oral 3 mg/day = 39-78 mg Sustenna, 6 mg = 117 mg Sustenna, 12 mg/day = 234 mg Sustenna; initiation of therapy: 234 mg on treatment day 1 followed by 156 mg 1 week later; administered in either the deltoid or gluteal muscle; then start monthly maintenance dose (may be administered 7 days before/after monthly time point) **3-month IM paliperidone used only after monthly IM paliperidone (Invega Sustenna) has been established as adequate treatment for at least 4 months. The last 2 doses of monthly IM paliperidone should be the same dosage strength before starting 3-month IM paliperidone	<u>Schizophrenia</u> Adolescents 12 to 17 years: Oral 3 mg once daily	Oral tablet: Yes Injectable formulations: No

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Quetiapine (seroquel; seroquel XR)	Oral Tablet, Immediate Release (IR): 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg Oral Tablet, Extended Release (ER): 50 mg, 150 mg, 200 mg, 300 mg, 400 mg	Bipolar disorder: Acute treatment (as monotherapy and as an adjunct to lithium or divalproex) of manic episodes or mixed episodes (ER tablet only) associated with bipolar I disorder; maintenance treatment of bipolar I disorder (as an adjunct to lithium or divalproex); acute treatment of depressive episodes associated with bipolar disorder Major depressive disorder (ER only): Adjunctive therapy to antidepressants for the treatment of major depressive disorder Schizophrenia: Treatment of schizophrenia	Obsessive compulsive disorder Delirium in the critically-ill patient Delusional parasitosis Generalized anxiety disorder Post-traumatic stress disorder Psychosis/agitation related to Alzheimer disease and other dementias Psychosis in Parkinson disease Tardive dyskinesia	<u>Bipolar disorder</u> Depressive episodes: Immediate release 300 mg daily Extended release 300 mg daily Acute Mania Episodes (monotherapy or as an adjunct to lithium or divalproex): Immediate release 400-800 mg daily Acute Mixed Episodes (monotherapy or as an adjunct to lithium or divalproex): Extended release 400-800 mg daily Maintenance therapy (adjunct to lithium or divalproex): Immediate release or extended release 400-800 mg daily <u>Major depressive disorder</u> (adjunct to antidepressants) Extended release 150-300 mg daily <u>Schizophrenia</u> Immediate release 150-750 mg daily in 2-3 divided doses Extended release 400-800 mg daily **Titrate 50-100 mg daily on day 1 and increase by 100 mg once daily **Switch from immediate release to extended release tablets at the equivalent total daily dose and administer once daily ***Dosage adjustment for concomitant therapy with strong CYP450 (3A4) inhibitor/inducer	<u>Bipolar disorder</u> Children ≥10 years and Adolescents ≤17 years Mania (monotherapy): Immediate release 400 to 600 mg daily, divided into 2-3 doses per day Extended release 400 to 600 mg once daily <u>Schizophrenia</u> Adolescents 13 to ≤17 years Immediate release 400 to 800 mg daily, divided into 2-3 doses per day Extended release 400 to 600 mg once daily **Titrate and Switching from ER to IR: Refer to adult dosing.	Oral tablet: Yes Extended release oral tablet: No

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Risperidone (Risperdal; Risperdal Consta; Risperdal M-TAB; Risperidone M-TAB)	Oral Solution: 1 mg/mL Intramuscular Suspension, Reconstituted: Risperdal Consta 12.5 mg, 25 mg, 37.5 mg, 50 mg Oral Tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg Oral Tablet, Dispersible: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg	<u>Oral</u> Schizophrenia: Treatment of schizophrenia Bipolar Disorder: Treatment of acute mania or mixed episodes associated with bipolar I disorder (as monotherapy in children or adults, or in combination with lithium or valproate in adults) Autistic Disorder: Treatment of irritability/aggression associated with autistic disorder <u>Injection</u> Schizophrenia: Treatment of schizophrenia Bipolar Disorder: Maintenance treatment of bipolar I disorder in adults as monotherapy or in combination with lithium or valproate	Delusional parasitosis Major depressive disorder Post-traumatic stress disorder Psychosis/agitation related to Alzheimer disease and other dementias Tourette syndrome	<u>Bipolar mania</u> Oral: 1 to 6 mg daily Intramuscular (Risperdal Consta): 25-50 mg every 2 weeks; dosage adjustments should not be made more frequently than every 4 weeks <u>Schizophrenia</u> Oral: 2 to 8 mg daily Intramuscular (Risperdal Consta): 25-50 mg every 2 weeks; dosage adjustments should not be made more frequently than every 4 weeks **Oral dose titrated by 1 mg daily in intervals ≥24 hours **Tolerability should be established with oral risperidone prior to initiating treatment with CONSTA **Oral risperidone (or other antipsychotic) should be administered with the initial injection of Risperdal Consta, continued x 3 weeks then discontinued	<u>Autism</u> Children ≥5 years and Adolescents Oral: <15 kg: Use with caution; specific dosing recommendations not available 15 to <20 kg: 0.5-3 mg/day once daily or in divided doses twice daily ≥20 kg: 0.5-3 mg/day once daily or in divided doses twice daily <u>Bipolar mania</u> Children and Adolescents 10-17 years Oral: 0.5 to 6 mg daily or in divided doses twice daily <u>Schizophrenia</u> Adolescents 13 to 17 years Oral: 1 to 6 mg daily or in divided doses twice daily ** Titrate: initial 0.25-0.5 mg daily; may increase dose to 0.5 mg daily after ≥4 days or 0.25 mg daily in ≥2-week intervals	Yes; except Intramuscular Consta injection

Agent	Preparations	Labeled Indications	Off-label Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Ziprasidone (Geodon)	Oral Capsule: 20 mg, 40 mg, 60 mg, 80 mg Intramuscular Solution Reconstituted: 20 mg	Schizophrenia: Treatment of schizophrenia Bipolar I Disorder: Treatment of acute manic or mixed episodes associated with bipolar disorder with or without psychosis; maintenance treatment of bipolar disorder as an adjunct to lithium or valproate Acute Agitation: Treatment of acute agitation in patients with schizophrenia	Major depressive disorder Psychosis/agitation related to Alzheimer disease and other dementias	Bipolar disorder (acute and maintenance as adjuncts to lithium or valproate) Oral: 40-80 mg twice daily Schizophrenia Oral: 20 - 100 mg twice daily Acute agitation (schizophrenia) Intramuscular: 10 mg every 2 hours or 20 mg every 4 hours (maximum: 40 mg daily); oral therapy should replace intramuscular administration as soon as possible	Not indicated	Capsule: Yes Solution: No

Key: DSC = discontinued, IM = intramuscular, IR = immediate release, ER = extended release

Table 2. Second-Generation Atypical Antipsychotic Agents FDA-Labeled Indications[1,2]

	Schizophrenia	Schizoaffective Disorder	Bipolar I Disorder	Major Depressive Disorder	Autistic Disorder	Tourette Disorder
Aripiprazole	X		X	X	X	X
Asenapine	X		X			
Brexpiprazole	X			X		
Cariprazine	X		X			
Clozapine	X					
Iloperidone	X					
Lurasidone	X		X			
Olanzapine	X		X			
Paliperidone	X	X				
Quetiapine	X		X	X		
Risperidone	X		X		X	
Ziprasidone	X		X			

Disease Overview

Mental illness is defined as any diagnosable mental disorder with sustained abnormalities in behavior, mood or thinking which result in impaired functioning and distress.[8]Diagnosable mental disorders may include anxiety disorders, mood disorders, personality disorders, attention deficit disorders, schizophrenia, addiction disorders and feeding/eating disorders.[3] The most commonly reported mental illnesses in adults in the United States (US) are anxiety and mood disorders, including depression and bipolar disorder.[8] The most commonly reported mental illnesses in adolescents in the US are depression and attention deficit disorders.[9] All mental illnesses can cause severe disruptions in activities of daily living and result in premature death. According to the World Health Organization (WHO), mental health disorders cause more patient disability than cancer, heart disease or any other illness.[8] In addition, mental health disorders are associated with increased rates of comorbid chronic diseases (including cardiovascular disease, diabetes, obesity, asthma, epilepsy and cancer), inappropriate use of medical care (including treatment nonadherence and increased emergency department visits), use of tobacco products, abuse of alcohol and other substances, increased rates of intentional and unintentional injuries and an overall increase in adverse health outcomes.[8] According to the Centers for Disease Prevention and Control (CDC), approximately 25% of all adults currently have a mental illness and up to 50% of adults will report a mental illness during their lifetime resulting in an economic burden of nearly $300 billion in the US (2002).[8] Increased access to mental health treatment services results in successful management of the mental health disorder, reduced rates of mortality and morbidity and improved health outcomes for comorbid chronic diseases.[8]

Schizophrenia

Schizophrenia is a psychiatric disorder characterized by abnormal thought processes, including delusions and hallucinations. The prevalence of schizophrenia is 0.5-1% across the world and 1.1% in the US.[10,11] In general, schizophrenia occurs more frequently in men than women and the average age of first onset of the disease is 21-27 years. The economic burden of schizophrenia in the US (~6.85 billion in 2004) results from the combined costs associated with increased rates of unemployment, lost productivity, morbidity and mortality in addition to direct healthcare costs.[10] Schizophrenia is associated with an increased rate of emergency department (ED) visits with almost 400,000 ED visits annually and an overall ED visit rate of 20.1 per 10,000 adults in the US. Public insurance organizations, including Medicaid and/or Medicare, are used to pay for ED visits related to schizophrenia more frequently than non-schizophrenia ED visits. Of the ED visits related to schizophrenia, about 50% result in either hospital admission (32.7%) or transfer to a psychiatric hospital (16.7%), a rate much higher than non-schizophrenia ED visits.[9] Schizophrenia is also associated with an increased risk for suicide; 33% of those diagnosed with schizophrenia will attempt suicide and up to 10% will eventually take their own lives.[10,12] Increased understanding of the disease and improving access to mental health services improves health outcomes and reduces the economic burden of schizophrenia.

Schizophrenia is defined as a mental disorder with abnormal thought processes, irregular emotional responsiveness, delusions (false beliefs) and hallucinations (hearing or seeing things not actually present).[10,11] Schizophrenia is a serious, chronic debilitating mental illness and the symptoms associated with the disorder make it very difficult for patients to work, form relationships or complete many daily activities of normal living. Schizophrenia symptoms are typically categorized as either “positive” symptoms or characteristics not usually seen in patients without the disorder (including delusions and hallucinations) and “negative” symptoms or

characteristics lacking in patients with the disorder (including lack of motivation and social relationships and a blunted affect). Schizophrenia is a complex disorder which may be considered a collection of different disorders. According to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5), formal diagnosis of schizophrenia requires the presence of at least two symptoms for at least 1 month with continuous signs of the disease for at least 6 months.[11, Harrisons] Patients exhibiting the symptoms of schizophrenia for less than 6 months may be diagnosed with *schizophreniform* disorder and patients with schizophrenia symptoms in combination with periods of mood disturbance may be diagnosed with *schizoaffective* disorder.[3] Some evidence suggests full psychosis occurs later in the disease development and early, intense therapeutic interventions may reduce overall disease severity.[11]

Treatment of schizophrenia may include medication therapy, psychological counseling and psychosocial interventions. Medication therapy includes antipsychotic agents, anti-anxiety medications and antidepressant therapies. Both the first-generation and second-generation antipsychotic agents have demonstrated efficacy in the treatment of schizophrenia and are the foundation of medication therapy. Unfortunately, the antipsychotic agents are also associated with numerous adverse effects, which may limit their use. For example, the first-generation agents are associated with increased rates of extrapyramidal symptoms (EPS) and the second-generation agents are associated with increased risks of metabolic adverse effects. Selection of an appropriate antipsychotic agent is based on patient-specific characteristics (age and disease severity, treatment history, comorbid conditions) and adverse event profile. In general, second-generation antipsychotic agents (such as quetiapine, risperidone, aripiprazole or ziprasidone) are recommended over the first-generation agents for first-time schizophrenia episodes due to reduced risk of neurologic adverse effects. For multiple-episode or relapse schizophrenia, treatment recommendations include increasing the dose of the current antipsychotic agent, switching to a different antipsychotic agent, assessing adherence and considering a switch to a long-acting injectable antipsychotic agent (such as olanzapine, aripiprazole, paliperidone or risperidone). Clozapine is the recommended therapy for patients with treatment-resistant schizophrenia. In general, treatment with 2 or more antipsychotic agents at the same time is not recommended and should be avoided, if possible. Benzodiazepines are recommended for treatment of schizophrenia-related agitation and antidepressants may be helpful in patients with schizophrenia and depression.[4-6,13-15]

Clinical guidelines for the treatment of schizophrenia include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia (2012, 2013, 2015)[4-6], the American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia (2004)[16], the National Institute for Health and Clinical Excellence (NICE) Psychosis and Schizophrenia in Adults: Treatment and Management (2014)[17] and the American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Schizophrenia (2013).[18] See Table 3 for a summary of the most current guideline recommendations. In general, the guidelines recommend treatment with a single antipsychotic agent but do not recommend one agent over another. Treatment with more than one antipsychotic agent should be avoided and clozapine is recommended in treatment-resistant schizophrenia disease. Limited evidence is available for the treatment of clozapine-resistant schizophrenia. A recent systematic review of randomized-controlled trials (2015) evaluating the efficacy of aripiprazole augmentation of

clozapine, reported increased efficacy in mitigating psychotic symptoms and reduced risk of cardiometabolic and agitation/akathesia effects with clozapine and aripiprazole combination therapy.[19] A double-blind, placebo-controlled study of 40 patients with schizophrenia (2014) reported ziprasidone augmentation of clozapine significantly reduced both positive and negative symptoms on the syndrome scale and did not increase overall cardiovascular risk (QT prolongation).[20] A comparative study of ziprasidone or risperidone augmentation of clozapine (2009) reported significant psychopathological improvements compared to baseline for both ziprasidone and risperidone with differences in adverse effects between the treatment groups (increased QT prolongation and reduced extrapyramidal symptoms with ziprasidone & increased serum prolactin levels with risperidone).[21] Additional clinical evidence evaluating clozapine augmentation with risperidone, quetiapine or ziprasidone is inconsistent and suggests no added benefit with dual therapy.[22-26]

The Schizophrenia Patient Outcomes Research Team (PORT, updated 2009) published evidence-based treatment recommendations based primarily on empirical data, which are the basis for many of the clinical practice guidelines mentioned above.[27] According to the recommendations, any antipsychotic agent (with the exception of clozapine or olanzapine, due to increased risk for adverse effects with these agents) is recommended as first-line treatment of schizophrenia at daily dosages of: 300-500 mg chlorpromazine (CPZ) equivalents for all first-generation agents or on the lower end of the dose ranges for the second-generation agents. In general, the initial choice of antipsychotic medication is based on individual preference, treatment history (including efficacy, adverse effects, adherence), medical history, risk factors, concurrent medications and long-term treatment planning. For maintenance therapy, continuation of the initial agent at the effective dose or switching to a long-acting injectable (LAI) agent in patients where injectable formulations are preferred to oral formulations is recommended. Treatment-responsive patients with an acute symptom episode generally require an increase in dose or switch to a different agent (including olanzapine). Clozapine 300-800 mg daily is recommended in patients with schizophrenia who have persistent, clinically significant positive symptoms after at least 2 trials of other antipsychotic agents, in patients who exhibit violent behaviors or in patients with suicidal thoughts or behaviors. In addition, psychosocial interventions including Assertive Community Treatment, supported employment and skills training, Cognitive Behavioral Therapy, family-based services and psychosocial interventions for tobacco, alcohol and substance use disorders demonstrate efficacy in reducing hospitalizations and homelessness in patients with schizophrenia.[27] A follow-up, retrospective, cohort study of the PORT recommendations in adult Medicaid beneficiaries with schizophrenia (n = 2132) was published in 2012.[28] According to this evidence, patients treated according to the PORT recommendations (including dose recommendations, frequent mental health visits, continuity of care) experienced reduced rates of mortality. An additional follow-up study of the PORT recommendations evaluated the rates of community mental health compliance with the PORT guidelines and reported high rates of adherence (>90%).[29]

Table 3. Current Clinical Practice Guidelines for the Treatment of Schizophrenia

Guideline	Recommendations
The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment	Treatment of Acute Positive Symptoms in Treatment-Responsive Patients: any antipsychotic agent other than clozapine with a daily dose of 300–1000 mg chlorpromazine equivalent first-generation agent OR aripiprazole 10–30mg,

Guideline	Recommendations
recommendations (2009)[27]	olanzapine 10–20 mg, paliperidone 3–15 mg, quetiapine 300–750 mg, risperidone 2–8 mg, ziprasidone: 80–160 mg Treatment of Acute Positive Symptoms in Patients with First-Episode Schizophrenia: any antipsychotic agent other than clozapine or olanzapine with a daily dose of 300–500 mg chlorpromazine equivalent first-generation agent OR lower half of recommended dosage range for all second-generation agents except quetiapine (500–600 mg/day) Maintenance Treatment in Treatment-Responsive Patients: continued agent/dose of antipsychotic treatment; long-acting injectable agents should be considered when the injectable formulation is preferred over oral therapy Treatment of Treatment-Resistant Schizophrenia: clozapine 300-800 mg daily for at least 8 weeks is recommended in patients who continue to experience symptoms after 2 antipsychotic trials Treatment of Special Populations: clozapine 300-800 mg daily for at least 8 weeks is recommended in patients with hostility or suicidality Psychosocial interventions including Cognitive Behavioral Therapy and interventions for tobacco, alcohol and substance use disorders are recommended

World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia (2012, 2013, 2015)[4-6]	• Antipsychotic agents are recommended as first-line therapy in all stages of schizophrenia
	  ○ Both first-generation and second-generation agents are equally effective in reducing psychotic symptoms
	  ▪ Second-generation agents: olanzapine, risperidone and quetiapine have the best evidence for first-episode patients
	  ▪ First-generation agent: haloperidol has the best evidence for first-episode patients
	  ▪ Side effects may vary between the agents and special attention should be given to motor, metabolic and cardiovascular side effects
	  ○ Lower antipsychotic dosages are recommended in first-episode schizophrenia
	  ○ Clozapine *is not* recommended for the first-line treatment in first-episode schizophrenia
	  ○ Clozapine *is* recommended in treatment-resistant schizophrenia
	  ▪ Switching to another second-generation agent, preferentially olanzapine or risperidone, is recommended in clozapine-resistant schizophrenia
	  ○ Limited evidence is available for the efficacy of combining two antipsychotics or an antipsychotic and another agent (mood stabilizer, anticonvulsant, etc.) in treatment-resistant schizophrenia
	  ○ Psychosocial interventions are recommended along with pharmacologic treatment

Psychosis and Schizophrenia in Adults: Treatment and Management 2014; National Institute for Health and Care Excellence (NICE)[17]	• First-line recommendation: a single antipsychotic agent
	  ○ Selection of antipsychotic agent should be based on patient characteristics and potential side effects
	  ○ Large loading doses are *not* recommended
	  ○ Combination antipsychotic therapy is *not* recommended

Guideline	Recommendations
	○ Injectable formations are recommended in patients with difficulty with adherence to oral therapy ○ Medication therapy should be continued for up to 1-2 years ○ Clozapine is recommended in patients with 2 antipsychotic trials (including one second generation antipsychotic) without significant improvement • The goal of medication therapy is to prevent relapse and maintain quality of life
American Psychiatric Association (APA): Practice Guideline for the Treatment of Patients with Schizophrenia (2004)[16]** ****"This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice"**	• Acute phase ○ First-line: aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone ▪ Clozapine is recommended in patients with suicidal behavior, hostility or aggression ▪ A second-generation agent is recommended in patients with tardive dyskinesia or sensitive to extrapyramidal side effects • Only use low-dose risperidone ▪ A second-generation agent is recommended in patients sensitive to prolactin elevations • Not clozapine or risperidone ▪ Aripiprazole or ziprasidone is recommended in patients sensitive to weight gain, hyperglycemia or hyperlipidemia ▪ Long-acting injectable therapy is recommended in patients with non-adherence to oral therapy ○ If inadequate response, switch to a new agent: aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone ○ If inadequate response to a second agent, switch again to a new agent: aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone ○ Clozapine is recommended in patients with persistent psychotic symptoms ○ Consider electroconvulsive therapy for persistent severe psychosis • Stabilization or maintenance phase ○ Continue with acute phase pharmacological and/or electroconvulsive therapy ▪ If intolerable side effects, switch to a new agent: aripiprazole, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone
The Texas Medication Algorithm Project (TMAP): Texas Implementation of Medication Algorithms (TIMA) Procedural Manual: Schizophrenia Module (2008)[30]	Stage 1: a low-dose second generation-agent is first-line Stage 2: a trial of a single first- or second-generation antipsychotic in patients who do not respond to initial therapy Stage 3: a trial of clozapine is recommended in patients without adequate response to two different antipsychotic trials or earlier in patients with a history of suicidal ideation, violence or comorbid substance abuse Stage 4: a trial of clozapine plus a first- or second-generation agent or

Guideline	Recommendations
	electroconvulsive therapy is recommended in clozapine-resistant patients Stage 5: another trial of a single first- or second-generation antipsychotic not tried in stages 1 or 2 is recommended in patients resistant to clozapine-augmented therapy Stage 6: combination therapy with a first- and second-generation agent, two second-generation antipsychotics, antipsychotic therapy with electroconvulsive therapy or antipsychotic agents with mood stabilizer is recommended in patients with continued antipsychotic-resistance

American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Schizophrenia (2013)[18]	Adequate treatment of schizophrenia requires the combination of pharmacological agents and psychosocial interventions
	
	Pharmacotherapy:
	• Antipsychotic agents are recommended for the treatment of psychotic symptoms
	  ○ First-line agents include first-generation and second-generation agents
	  ▪ The second-generation agents may be more helpful for negative symptoms
	  ○ The use of an antipsychotic agent requires:
	  ▪ informed consent
	  ▪ documentation of target symptoms
	  ▪ baseline and follow-up laboratory monitoring
	  ▪ documentation of treatment response
	  ▪ monitoring for known side effects
	  ▪ adequate therapeutic trials (appropriate dose for 4-6 weeks)
	  ○ First-episode patients should receive some maintenance treatment for 1 to 2 years
	  ○ Some patients may benefit from the use of adjunctive agents (including antiparkinsonian agents, mood stabilizers, antidepressants, benzodiazepines)
	
	Psychosocial Interventions:
	• Ongoing education about the illness and treatment options
	• Social skills training
	• Relapse prevention
	• Basic life skills training
	• Problem-solving skills
	• Psychoeducational therapy for the family

Bipolar Disorder

Bipolar disorder (or manic-depressive disorder) is a mood disorder characterized by episodes of depression and mania.[31] The prevalence of bipolar disorder is 0.4-1.4% across the world and 4% in the US.[10,32] In general, bipolar disorder occurs more frequently in women than men and the average age of first onset of the disease is 25 years. Bipolar disorder is the most expensive mental health disorder with costs reportedly double those of depression per affected individual. The economic burden of bipolar disorder in the US results from indirect costs due to lost productivity resulting from absenteeism and presenteeism in addition to direct healthcare costs.[10] Bipolar disorder is also associated with an increased rate of substance abuse, legal and financial complications, relationship difficulties, self-harm and serious suicide attempts. Successful disease management and early treatment intervention can help to improve health outcomes and reduce the economic burden of bipolar disorders.[10]

The depression-mania cycles associated with bipolar disorder are unpredictable with mania episodes typically emerging over a period of days to weeks and persisting up to several weeks or months. Mania is defined as clearly elevated moods with unrestrained behaviors lasting at least a week with at least 3 symptoms which may include irritability, grandiosity, sleeplessness, pressure talking, distractibility or engaging in activities with a high potential for adverse consequences. Clinical evidence suggests anger and agitation are the most common symptoms in pediatric patients while disordered thought content occurs most frequently in adult patients.[33] In severe mania, symptoms similar to those seen in schizophrenia, including delusions and paranoid thinking, may present. The depression episodes are defined as a persistent low mood including lack of positive affect and anhedonia causing impairment for greater than 2 weeks. In bipolar II disorder patients may lack the full criteria for mania and the recurrent depression episodes are instead separated by hypomania episodes with mild activation and increased energy.[3,31,Harrisons]

Treatment of bipolar disorder includes psychotherapy and medication therapy (mood stabilizers and antidepressant medications). Mood stabilizers may include lithium, anticonvulsant therapies and antipsychotic agents. Lithium is typically the first-line agent and has demonstrated efficacy in the treatment of bipolar disorder with a response rate of 70-80%, beneficial effects within 1-2 weeks and prophylactic effects. Antidepressants are effective in treating breakthrough depression episodes but may precipitate mania or accelerate cycle frequency. Recent clinical evidence suggests mood stabilizers demonstrating efficacy for mania are also efficacious for mixed episodes, reducing the need for antidepressant therapy.[34] Antipsychotic agents (such as aripiprazole, asenapine, cariprazine, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone) may be used alone or in combination with other mood stabilizers or antidepressants to maintain mood stability, control agitation or treat bipolar disorder in patients experiencing loss of efficacy with lithium therapy.[3,CDC, 2016 #2670]

Clinical guidelines for the treatment of bipolar disorder include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Bipolar Disorder (2013)[35-37], the American Psychiatric Association Practice Guideline for the Treatment of Patients with Bipolar Disorder (2002)[38], the National Institute for Health and Clinical Excellence (NICE) Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care (2014)[39] and American

Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007).[40] See Table 4 for a summary of the most current guideline recommendations. In general, the guidelines recommend treatment for acute mania episodes and acute depression episodes and maintenance therapy in patients at high risk for recurrence or severe disease. For selection of pharmacotherapy in the treatment of acute mania or depression episodes, factors to consider include: symptoms (such as euphoric, mixed, psychotic, suicidality), severity, treatment history, adverse effect profile and patient preference.[35-37]

Medication therapy for acute mania episodes (lithium, valproate, aripiprazole, risperidone, ziprasidone, etc.) should be continued until full remission.[35-37,39,40] If no response or only a partial response is achieved after 2 weeks of therapy, increase the dose of the medication or switch to another agent. Combination therapy is recommended in patients with continued treatment-resistance to a single agent. In patients with severe mania, clozapine or electroconvulsive therapy (ECT) may be indicated. Recommendations for antidepressant therapy in the treatment of acute depression episodes are inconsistent. In general, medication therapy for acute depression episodes (antidepressants, lithium, quetiapine, olanzapine, lamotrigine, etc.) should be provided in an established treatment setting, in combination with behavioral therapy and regularly assessed for both efficacy and adverse effects. Before initiation of treatment for acute depression, all other potential medical causes should be ruled out and caffeine, alcohol and other substances should be discontinued. Of note, the full therapeutic effects of antidepressant therapy, lithium and lamotrigine may take several weeks; additional symptomatic treatment with benzodiazepines during the first few weeks of an acute bipolar episode may be required. Maintenance therapy is recommended in patients with three or more acute episodes, two acute episodes and a positive family history for bipolar disorder or in patients with severe disease.[35-37,39,40]

Table 4. Current Clinical Practice Guidelines for the Treatment of Bipolar Disorder

Guideline	Recommendations
World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorder (2013)[35-37]	Treatment of an acute mania episode, any one of the following: • aripiprazole 15-30 mg daily • lithium 600-1200 mg daily (serum level 0.8-1.3 mmol, only if chronic treatment is being considered) • risperidone 2-6 mg daily • valproate 1200-3000 mg daily (loading dose 20-30 mg/kg; serum level 75-100 mg; not preferred in women of childbearing age) • ziprasidone 80-160 mg daily Treatment of acute depressive episode: • best evidence: quetiapine 300-600 mg daily • good evidence: fluoxetine/olanzapine combination therapy • fair evidence: bupropion, fluoxetine, imipramine, sertraline, tranylcypromine, venlafaxine in combination with a antimanic agent; lithium monotherapy; lithium in combination with lamotrigine Maintenance treatment, best evidence for: • aripiprazole

Guideline	Recommendations
	• lamotrigine • lithium • quetiapine
National Institute for Health and Clinical Excellence (NICE) Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care (2014)[39]	<u>Adults</u> Mania • haloperidol, olanzapine, quetiapine or risperidone • lithium alone or in combination with haloperidol, olanzapine, quetiapine or risperidone Depression • fluoxetine/olanzapine, quetiapine, olanzapine, lamotrigine • lithium alone or in combination with fluoxetine/olanzapine, quetiapine, olanzapine, lamotrigine Maintenance Therapy • lithium alone or in combination valproate • valproate, olanzapine, quetiapine <u>Precautions</u> • There is an increased risk for side effects in young patients ○ Antipsychotic treatment is not recommended for longer than 12 weeks in young patients • For treatment of depression in young patients, a structured psychological intervention for at least 3 months is recommended • Lithium and/or valproate should not be initiated in primary care • Do not use lamotrigine for acute mania or mixed episode
American Psychiatric Association (APA): Practice Guideline for the Treatment of Patients with Bipolar Disorder (2002)[38]** ****"This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice"**	Acute manic or mixed episodes • Adjunctive antipsychotic therapy should be considered in manic or mixed manic episodes with psychotic features ○ Second-generation agents are recommended over first-generation agents due to side effect profile Acute depressive episodes • Adjunctive antipsychotic therapy or electroconvulsive therapy is recommended in acute depressive episodes with psychotic features Maintenance • Adjunctive antipsychotic therapy should be closely monitored, reassessed and slowly tapered, if indicated Acute rapid cycling • Combination therapy with a second-generation antipsychotic may be indicated
Veterans Affairs/Department of Defense (VA/DoD): Clinical Practice Guideline for Management of Bipolar Disorder in Adults (2010)[41]	Mania: Agents most likely to be beneficial include lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone; lithium or valproate may be combined with an atypical antipsychotic Mixed episode: Agents most likely to be beneficial include valproate, carbamazepine, aripiprazole, olanzapine, risperidone or ziprasidone Depression: Agents most likely to be beneficial include quetiapine, lamotrigine,

Guideline	Recommendations
	lithium, olanzapine/fluoxetine, olanzapine Notes: **Treatment response should be evaluated at 4 to 8 weeks and periodically until full remission **Patients who have failed monotherapy for mania: consider switching to another monotherapy or combining a non-antipsychotic mood stabilizer (lithium or valproate) with a second generation antipsychotic **Treatment of severe mania or mixed episode: clozapine with valproate or lithium ** Treatment of severe depression: clozapine
The Texas Medication Algorithm Project (TMAP): Texas Implementation of Medication Algorithms (TIMA) Procedural Manual: Bipolar Disorder Algorithms (2007)[42]	Hypomania or mania <u>Stage 1</u> Euphoric symptoms: lithium, valproate, aripiprazole, quetiapine, risperidone, ziprasidone Mixed symptoms: valproate, aripiprazole, risperidone, ziprasidone <u>Stage 1b</u> olanzapine and carbamazepine are alternatives <u>Stage 2</u> combination therapy with two: lithium, valproate, olanzapine, quetiapine, risperidone, or ziprasidone (not 2 antipsychotics) <u>Stage 3</u> a different combination than in Stage 2, with additional options: carbamazepine, oxcarbazepine, aripiprazole, a first-generation antipsychotic <u>Stage 4</u> clozapine or a 3-drug combination including lithium, an anticonvulsant mood stabilizer (valproate, carbamazepine, or oxcarbazepine) an atypical antipsychotic agent Depression <u>Stage 1</u> lamotrigine monotherapy for patients without a recent and/or severe history of mania OR lamotrigine plus a mood stabilizer <u>Stage 2</u> quetiapine monotherapy or olanzapine/fluoxetine combination treatment <u>Stage 3</u> evidence-based medicine is limited
American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007)[40]	Standard therapy (based on adult literature): lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated; antidepressants may be used as adjunctive therapy for bipolar depression The choice of medication should be based on • evidence of efficacy • illness phase • presence of confounding symptoms • side effects • patient's medication response history • patient and family preferences Additional notes • clozapine or electroconvulsive therapy are reserved for treatment-refractory

Guideline	Recommendations
	cases • maintenance medication therapy may be recommended to prevent relapse • baseline and follow-up review of symptoms/efficacy, adverse effects and laboratory monitoring is recommended • 6-8 week trial of a mood-stabilizing agent is recommended before switching agents or adding an additional agent • psychotherapy is recommended as part of a comprehensive treatment plan

Major Depressive Disorder

The mood disorders (including depressive disorder, bipolar disorder, etc.) affect approximately one in ten adult Americans.[43] Major depressive disorder is the most common of the mood disorders, affecting nearly 15% of US adults.[44] In 2004, depression was listed as the third most common cause of disease burden across the world.[10] In general, depression occurs more frequently in women than men, in the 40-59 year age range and in patients living below the poverty level. Depressive disorder is linked to increased rates of chronic disease, health care utilization and impaired activities of daily living. Almost half of all patients with depression experience inabilities to maintain healthy work, home and social habits. The economic burden of depression in the US (~$83.1 billion in 2000) results from the combined costs associated with increased rates of indirect costs (unemployment, lost productivity, etc.) in addition to direct healthcare costs.[9,45] Depression is frequently underdiagnosed and, even more frequently, depression is inadequately treated. Improving disease education and increasing access to care will help to improve clinical outcomes and save costs.[3]

Depression is a serious mental disorder characterized by changes in cognitive and physical behaviors with a loss of pleasure in enjoyable activities.[3] Major depression is defined as the presence of at least 5 symptoms during a minimum of a 2 week period which reflect a change in previous functioning and cause distress or impairment in normal activities. Symptoms associated with a depression episode must include sadness and/or loss of interest or pleasure and may also include significant unexplained weight loss, insomnia or hypersomnia, agitation, fatigue, feeling worthless or excessive guilt, reduced ability to concentrate and recurrent thoughts of death. In some patients (< 2% of the general population), depression may not be clearly associated with acute distress, impairment or change from previous functioning. Dysthymic disorder is defined as a persistent depressive mood with chronic (≥2 years), ongoing symptoms which tend to be less severe and/or numerous.[3]

Drug therapy is the foundation of the medical management of the mood disorders. Before the introduction of the second-generation antidepressants, drug therapy was limited to tricyclic antidepressants and monoamine oxidase inhibitors, known collectively as the first-generation antidepressants. The first generation antidepressants are associated with many intolerable adverse effects (sedation and anticholinergic effects) and are no longer agents of choice for treating depressive disorders. As a result, the second-generation antidepressants are one of the leading drug classes in the US pharmaceutical market and accounted for $10.9 billion in US prescription sales in 2003.[9,45] Clinical evidence suggests the most efficacious treatment for depression includes a combination of psychological therapy and medication therapy for at least 6-8 weeks with a treatment plan to reduce the risk of disease/symptom recurrence.[9] Almost half

of all patients being treated for depression by their primary care provider will discontinue their medication therapy within a month, unless proper education and a treatment plan is provided. Selection of an antidepressant agent should be based on treatment history, comorbid conditions and patient preference. In patients demonstrating suicidal ideation, for example, drug selection should be based on agents with low toxicity if taken in overdose.[3]

Clinical guidelines for the treatment of depression include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders (2013)[46], the American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder (2010)[47], the National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition and management (2009)[48] and American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007).[49] See Table 4 for a summary of the most current guideline recommendations. In general, the guidelines recommend use of a second-generation antidepressant for the treatment of depression. First-line agents typically include those for which the patient has had a previous positive response or a family history of a positive response. If only a partial response is achieved at 6-8 weeks, referral to a mental health specialist is recommended. Partial responders should receive an alternative antidepressant, a combination of antidepressant agents or adjunctive treatment with another class of medications including lithium, thyroid hormone, atypical antipsychotic agent or dopamine agonist. A large randomized controlled trial examining Sequenced Treatment Alternatives to Relieve Depression (STAR*D) did not report any differences in efficacy between the adjunctive medication classes.[50] Medication therapy should be adjusted until full remission is achieved and treatment should be continued for an additional 6-9 months to prevent relapse. Chronic maintenance therapy is recommended in patients with two or more depression episodes. Cognitive behavioral therapy is recommended for all patients with depressive disorder.[3]

Table 5. Current Clinical Practice Guidelines for the Treatment of Depressive Disorders

Guideline	Recommendations

World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorder (2013)[47]	• Medication therapy in combination with psychological counseling is recommended
	• A treatment plan and disease/medication education are recommended for all patients
	• Antidepressant agents are recommended as first-line
	  ○ No single class of antidepressants has proven to be more effective than another
	  ▪ Amitriptyline, clomipramine and venlafaxine have demonstrated increased efficacy in severely depressed hospitalized patients
	• Second- (bupropion, trazodone) and third- (SSRI, SNRIs, mirtazapine) generation antidepressants are generally better tolerated than the older agents
	• In treatment-resistant patients: increasing the dose, switch to another antidepressant agent, combine two antidepressants, augmenting the antidepressant with other agents (best evidence for aripiprazole, lithium, quetiapine)

National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition	<u>Mild-Moderate Disorder</u> First-line: low-intensity psychosocial intervention Second-line: antidepressant therapy (typically SSRI) OR a high-intensity psychosocial

Guideline	Recommendations
and management (2009)[48]	intervention <u>Moderate-Severe Disorder</u> First-line: combination antidepressant therapy and a high-intensity psychological intervention <u>Antidepressant agents</u> • SSRIs have a favorable risk-benefit ratio • Fluoxetine, fluvoxamine and paroxetine are associated with increased risk of drug interactions • Venlafaxine and tricyclic antidepressants are associated with increased risk of death from overdose • Monoamineoxidase inhibitors (MAOIs) should only be prescribed by specialists • In treatment-resistant patients, increase dose or switch to another antidepressant

American Psychiatric Association (APA): Practice Guideline for the Treatment of Patients with Major Depressive Disorder (2010) [49]	<u>Acute phase</u>
	First-line: antidepressant medication (SSRI, SNRI, bupropion, mirtazapine
	• The effectiveness of antidepressant medications are comparable and initial selection is based on adverse effect profile, prior treatments, cost and patient preference
	  ○ If side effects occur, lower dose or switch agents
	  ○ If no response or partial response: increase dose, switch agents or augmenting the antidepressant with another antidepressant or a nonantidepressant medication (lithium, thyroid hormone or a second generation antipsychotic)
	
	<u>Continuation phase</u>
	Continue successful treatment for 6-9 months and monitor for signs of relapse
	
	<u>Maintenance phase</u>
	Continue successful treatment in patients with three or more depressive episodes or with additional risk factors for relapse
	
	<u>Discontinuation of treatment</u>
	Taper the medication over the course of at least several weeks
	
	<u>Other notes</u>
	Combination of antipsychotic and antidepressant medications is recommended in patients with psychotic symptoms

Institute for Clinical Systems Improvement (ICSI): Major Depression in Adults in Primary Care (2011)[51]	Recommended pharmacotherapy: SSRIs, venlafaxine, duloxetine, desvenlafaxine, mirtazapine, bupropion Other options: Secondary Amine Tricyclics (TCAs), Monoamine Oxidase Inhibitors (MAOIs) Augmentation therapy: bupropion, buspirone, mirtazapine, triiodothyronine (T3), stimulants, TCA-SSRI combination, lithium, atypical antipsychotics

Guideline	Recommendations
	**Recommended in patients with treatment-resistant or partially-responsive disease and referral to a mental health specialist is advised
Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults (2009)[52]	Selection of an antidepressant agent should be based on disease severity, comorbid conditions, adverse effect profile, treatment history, potential drug–drug interactions, patient preference and cost; Use of antidepressant should be accompanied by patient education, close monitoring (1-4 weeks) and self-management techniques First-line recommendations Bupropion, Citalopram, Desvenlafaxine, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Milnacipran, Mirtazapine, Paroxetine, Sertraline, Venlafaxine Second-line recommendations Amitriptyline, clomipramine and other tricyclic antidepressant (TCA) agents; Quetiapine; Selegiline; Trazodone Third-line recommendations Phenelzine, Tranylcypromine
American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007)[49]	• A confidential relationship should be maintained with the child or adolescent • Psychiatric assessments should routinely be made • Treatment should always include an acute and continuation phase, some may require maintenance treatment First-line: supportive psychotherapy Second-line: psychotherapy and/or antidepressants o Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used pharmacotherapy in pediatric patients o Clinical response should be assessed at 4-week intervals ▪ If inadequate response, increase dose o Treatment should be continued for 6-12 months o Atypical antipsychotics, combined with SSRIs, are recommended as the treatment of choice for depressed psychotic pediatric patients

Key: SSRI – selective Serotonin Reuptake Inhibitor, serotonin norepinephrine reuptake inhibitor - SNRI

Autistic Disorder

Autism spectrum disorder (ASD) is a developmental disorder with a wide range of disabilities, resulting in social and behavioral challenges.[53] In general, Autism occurs more frequently in boys than girls (about 4.5 times more frequently) and can be detected as early as 18 months or younger. The CDC estimates autism occurs in 1/68 children in the US. Patients with ASD are at increased risk of seizure disorders and up to 30% of patients have a concurrent epilepsy diagnosis. ASD specifically refers to several conditions including autistic disorder, pervasive developmental disorder or Asperger syndrome, all of which may be characterized by intellectual disability, language impairment, repetitive behaviors, failure to make eye-contact and difficulties with social interaction.[54] For patients with ASD, learning abilities may range from gifted to severely challenged and impairment of activities of daily living may be minimal to severe. Treatment of ASD may include behavior therapy, dietary restrictions, medication therapy

and some complementary/alternative medicines.[53] Clinical evidence demonstrates early intervention services in patients with ASD, starting as early as 36 months, improve a child's development. Early intervention services may include speech therapy and special education. Medication therapy may be used in addition to behavioral therapy to treat attention deficit symptoms, comorbid depression or seizure disorders. Currently, aripiprazole and risperidone are FDA-approved agents labeled for use in ASD. Other agents which have demonstrated efficacy include selective serotonin re-uptake inhibitors (SSRIs), stimulants, benzodiazepines and anticonvulsant agents.[55] Guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP, 2014)[56] recommend medication therapy for symptoms that interfere with educational interventions or for symptoms that cause distress to the individual. According to the guidelines, antipsychotic agents (haloperidol is the most extensively studied), SSRIs, TCAs, lithium and anxiolytics may be indicated. Potential adverse effects should be considered and monitored regularly.[56]

Tourette's Disorder

Tourette syndrome (TS) is an inherited, neurologic, childhood disorder.[57] The prevalence of TS is 1-30/1000 population across the world and 1/1000 population in the US.[8]0} Tourette syndrome occurs more frequently in boys than girls (3 times more frequently), in the later adolescent years (ages 12-17 years) and in non-Hispanic white persons. In addition, up to 80% of those diagnosed with TS also have a diagnosis for a second mental health or neurodevelopmental condition including attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), depression or anxiety. In general, Tourette syndrome is characterized by tics or repetitive, involuntary movements/sounds. The tics may be classified as simple (sudden and brief) or complex (movements involving several muscle groups). Tics may be worsened with excitement or anxiety and the most dangerous and disabling tics are those which result in self-harm. In general, medication therapy is not required for the treatment of tics. However, antipsychotic agents (haloperidol, aripiprazole, risperidone) and alpha-adrenergic agonists (clonidine and guanfacine) may be used to suppress tics in patients with reduced functioning, stimulants may be indicated in patients with concurrent ADHD and SSRIs may be used to treat OCD symptoms. The European Society for the Study of Tourette Syndrome (ESSTS, 2011) recommends risperidone as first-line treatment in patients requiring treatment to control tics. According to the guidelines, aripiprazole may be used in refractory cases and is associated with a reduced risk of weight gain compared to risperidone. Treatment with clonidine is recommended in patients with comorbid ADHD.[58] Less than 15% of those diagnosed with TS in adolescence will continue to have tic symptoms into adulthood.[57]

Pharmacology

The mechanism of action of the antipsychotic agents appears to be postsynaptic blockade of dopamine D2 and serotonin 5-HT2A receptors, though the specific mechanism of action is not fully known.[3,59] There are four different central dopamine tracts in the brain, namely the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular tracts. Differences in binding affinity between the antipsychotic agents for each dopamine tract result in differences in pharmacologic actions between the agents. Rate of dissociation from D2 receptors also appears to have an effect on antipsychotic effect, with rapid rates associated with greater antipsychotic effects.[3,59]

The dopamine receptors in the mesolimbic tract are thought to be responsible for the positive symptoms in schizophrenia.[3,59] Atypical antipsychotics are considered mesolimbic specific, though blockade of other receptors does occur. The dopamine receptors in the mesocortical tract are known to affect executive functions and higher-order thinking, and may be responsible for the negative symptoms associated with schizophrenia. Dopamine receptors in the nigrostriatal tract affect body movement and development of extrapyramidal symptoms (EPS) increase when >80% of these receptors are blocked. Antipsychotic effects are exhibited when approximately 65% of these receptors are blocked. The dopamine receptors in the tuberoinfundibular tract affect the anterior pituitary and release of prolactin, which can lead to hyperprolactinemia when blocked. The side effect profile of each atypical antipsychotic relates to the specific binding capacity of each agent in the four different dopamine tracts.[3,59]

The atypical antipsychotics have a greater affinity for 5-HT2A receptors than the first-generation antipsychotic agents, which may be associated with the reduced risk of EPS and improvement in negative symptoms.[3,59] Most atypical antipsychotics bind to approximately 80% of cortical 5-HT2A receptors, which helps to regulate the release of dopamine. Other receptors affected by atypical antipsychotics include dopamine D1, α-1 adrenergic, muscarinic M1, and histamine H1. Blockade of these receptors usually results in additional adverse effects instead of improvement in efficacy. Histamine H1 blockade results in more sedation, whereas blockade of muscarinic M1 can cause anticholinergic effects. Alpha-1 adrenergic blockade can result in orthostatic hypotension and sexual dysfunction.[3,59]

Table 6. Affinity for Receptor Types[3,59]

Atypical Agent	D_1	D_2	5-HT_2	α-1	M_1	H_1
Aripiprazole	+	+++	++	++	-	+
Asenapine	+++	+++	+++	+++	-	++
Brexpiprazole	-	+++	+++	+++	-	-
Cariprazine	-	+++	++	+	-	+
Clozapine	++	++	+++	+++	+++	+
Iloperidone	+	+++	+++	++	-	+
Lurasidone	-	+++	+++	++	-	-
Olanzapine	++	++	+++	++	+++	++
Paliperidone	-	+++	+++	+++	-	+
Quetiapine	-	+	++	+++	+	+
Risperidone	-	+++	+++	+++	-	+
Ziprasidone	U	++	+++	++	-	+

Key: U = unknown; - = none; + = minimal; ++ = moderate; +++ = high

Table 7. Pharmacokinetic Properties of the Second-Generation Atypical Antipsychotic Agents[1,2,60]

Agent	Absorption	Distribution	Metabolism	Excretion	Half-life elimination
Oral					
Aripiprazole (Abilify)	Tmax: 3-5 hours BA: 87%	Vd: 4.9 L/kg Pb: 99%	CYP2D6, CYP3A4 Active metabolite: dehydro-aripiprazole	Feces: 55% Urine: 25%	75-94 hours
Asenapine (Saphris)	Tmax: 0.5-1.5 hours BA: 35%	Vd: 20-25 L/kg Pb: 95%	CYP1A2, UGT1A4	Urine: 50% Feces: 40%	24 hours
Brexpiprazole (Rexulti)	Tmax: 4 hours BA: 95%	Vd: 1.56 L/kg Pb: 99%	CYP3A4, CYP2D6	Feces: 46% Urine: 25%	91 hours
Cariprazine (Vraylar)	Tmax: 3-6 hours BA: N/A	Vd: N/A Pb: 91-97%	CYP3A4 Active metabolites: DCAR DDCAR	Urine: 21%	2-4 days DDCAR: 1-3 weeks
Clozapine (Clozaril, Versacloz, FazaClo)	Tmax: 2.2-2.5 hours BA: 50-60%	Vd: 6 L/kg Pb: 97%	CYP2D6, CYP1A2, CYP3A4 Active metabolite: N-desmethylclozapine	Urine: 50% Feces: 30%	12 hours
Iloperidone (Fanapt)	Tmax: 2-4 hours BA: 96%	Vd: 1340-2800 L Pb: 95%	CYP3A4, CYP2D6 Active metabolites: P88 P95	Urine: 45-58% Feces: 20-22%	18-33 hours P88: 26-37 hours P95: 23-31 hours
Lurasidone (Latuda)	Tmax: 1-3 hours BA: 9-19%	Vd: 6173 L Pb: 99%	CYP3A4 Active metabolites: ID-14283 ID-44326	Feces: 80% Urine: 9%	18 hours
Olanzapine (Zyprexa, Zyprexa Zydis)	Tmax: 6 hours 40% removed via first pass metabolism	Vd: 1000 L Pb: 93%	CYP1A2, CYP2D6	Urine: 57% Feces: 30%	21-54 hours
Paliperidone (Invega)	Tmax: 24 hours BA: 28%	Vd: 487 L Pb: 74%	CYP2D6, CYP3A4	Urine: 51-67%	23 hours Renal impairment: 24-51 hours
Quetiapine (Seroquel, Seroquel XR)	Tmax (IR): 1.5 hours Tmax (ER): 6 hours BA: 100%	Vd: 10 L/kg Pb: 83%	CYP3A4 Active metabolites: norquetiapine 7-hydroxyquetiapine	Urine: 73% Feces: 20%	6-7 hours Norquetiapine: 12 hours

Agent	Absorption	Distribution	Metabolism	Excretion	Half-life elimination
Risperidone (Risperidal, Risperdal M-Tab)	Tmax: 1-2 hours BA: 70%	Vd: 1-2 L/kg Pb: 72-90%	CYP2D6 Active metabolite: 9-hydroxyrisperidone	Urine: 70% Feces: 14%	3-20 hours 9-hydroxyrisperidone: 21-30 hours
Ziprasidone (Geodon)	Tmax: 6-8 hours BA: 60%	Vd: 1.5 L/kg Pb: 99%	CYP3A4, CYP1A2 Active metabolites: BITP sulphoxide BITP-sulphone ziprasidone sulphoxide S-methyl-dihydroziprasidone	Feces: 66% Urine: 20%	7 hours
Injectable					
Aripiprazole (Abilify Maintena)	Tmax: 5-7 days	Vd: 4.9 L/kg Pb: 99%	CYP2D6, CYP3A4	Feces: 55% Urine: 25%	30-47 days (dose-dependent)
Olanzapine (Zyprexa, Zyprexa Relprevv)	Tmax (short): 15-45 minutes Tmax (long): 1 week	Vd: 1,000 L Pb: 93%	CYP1A2, CYP2D6	Urine: 57% Feces: 30%	Short: 21-54 hours Long-acting: 30 days
Paliperidone (Invega Sustenna)	Tmax: 13 days	Vd: 391 L Pb: 74%	CYP2D6, CYP3A4	Urine: 80% Feces: 11%	25-49 days
Paliperidone (Invega Trinza)	Tmax: 30-33 days	Vd: 1960 L Pb: 74%	CYP2D6, CYP3A4	Urine: 80% Feces: 11%	Deltoid: 84-95 days Gluteal: 118-139 days
Risperidone (Risperdal Consta)	Tmax: 29-31 days	Vd: 1-2 L/kg Pb: 72-90%	CYP2D6 Active metabolite: 9-hydroxyrisperidone	Urine: 70% Feces: 14%	3-6 days
Ziprasidone (Geodon)	Tmax: 60 minutes	Vd: 1.5 L/kg Pb: 99%	CYP3A4, CYP1A2 Active metabolites: BITP sulphoxide BITP-sulphone ziprasidone sulphoxide S-methyl-dihydroziprasidone	Feces: 66% Urine: 20%	2-5 hours

Key: Tmax: time to max concentration; BA: bioavailability; Pb: protein binding; Vd: volume of distribution; IM: intramuscular; ER: extended release; IR: immediate release

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database, the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE, evaluating efficacy of the second-generation atypical antipsychotic agents are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Non-comparative and placebo-controlled trials[34,61-82] [19,61,64,67,71,72,77,78,83-108] and trials comparing monotherapy with combination regimens or first-generation antipsychotic agents with second generation antipsychotic agents are excluded.[19,20,109-127] The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as: pharmacologic characteristics[128-155], adverse effects[63,91,96,156-195], adherence[196-201], quality of life[202-204], metabolic effects[137,205] or cost analysis.[206-209]
- Individual trials comparing the second-generation atypical antipsychotic agents in dose-finding studies or in healthy volunteers.[67,80,135,138,145,159,202,210-227]
- Individual clinical trials evaluating formulations or indications not currently approved in the US or clinical trials without access to the full article.[62,86,197,216,228-271] [74,233,234,272-277]

Clinical Efficacy

An Oregon Health and Science University Drug Class Review on the Atypical Antipsychotic Agents was published in 2010.[45] The drug class review includes a summary of the guideline recommendations, systematic reviews and comparative clinical trials evaluating the safety and efficacy of the agents. A summary of the clinical evidence is provided below. For this report, a PubMed and Cochrane Library literature search for systematic reviews and randomized controlled trials (RCTs) was conducted for trials published 1/2010-2/2016. The Agency for Healthcare Research and Quality (AHRQ), the FDA website (including product labeled information), Micromedex and Lexicomp were also searched for safety information, systematic reviews, clinical trials and guidelines. A summary of this evidence can be found in evidence tables in the appendix of this document as well as in the second half of the clinical efficacy section of this report.

Summary of the Oregon Health and Science University Atypical Antipsychotic Drug Class Review, July 2010[45]

Schizophrenia

All of the atypical antipsychotics are labeled for the treatment of schizophrenia. The clinical efficacy and effectiveness of the atypical antipsychotics were compared in 105 clinical head-to-head trials in patients with schizophrenia. In general, no differences in efficacy or effectiveness between the atypical antipsychotics in the treatment of

schizophrenia were found. Some evidence suggests a reduced risk of rehospitalization with olanzapine and a reduced risk of relapse with olanzapine when compared to quetiapine or risperidone, although study results are conflicting. In multiple trials, clozapine and olanzapine resulted in lower rates of discontinuation due to either lack of efficacy or adverse events. Limited evidence suggests clozapine reduces suicidality but results in more discontinuations due to adverse events. Overall, good-quality trial evidence found no differences in short-term efficacy between the atypical antipsychotics.

Special Populations: Limited evidence exists for the use of atypical antipsychotics in the treatment of schizophrenia in special populations. One study found clozapine and olanzapine were more effective when treating schizophrenia symptoms in women when compared with men. Differences between races were not found.

Bipolar Disorder

Six of the nine atypical antipsychotics are labeled for the treatment of bipolar disorder: aripiprazole, asenapine, olanzapine, quetiapine, risperidone, and ziprasidone. The clinical efficacy and effectiveness of the atypical antipsychotics were compared in five clinical head-to-head trials and 7 comparative observational studies in patients with bipolar disorder. In one trial, quetiapine use resulted in fewer mental health-related hospitalizations when compared to risperidone and olanzapine. Adjunctive treatment with aripiprazole was found to increase the time until hospitalization when compared to ziprasidone, olanzapine, quetiapine, or risperidone. In one observational study, olanzapine was associated with significantly improved compliance when used as monotherapy, but significantly reduced compliance when used as adjunctive therapy. Overall, no significant differences were found between risperidone, asenapine, and olanzapine in quality of life, remission, and response outcomes.

Special Populations: Limited evidence exists for the use of atypical antipsychotics in the treatment of bipolar disorder in special populations. One study found olanzapine and risperidone had similar response rates in treatment of bipolar disorder in children and adolescents.

Other Disorders

Four of the nine atypical antipsychotics are labeled for the treatment of other mental health disorders: aripiprazole, olanzapine, quetiapine, and risperidone. The clinical efficacy and effectiveness of the atypical antipsychotics were compared in 7 clinical head-to-head trials in patients with behavioral and psychological symptoms of dementia. In these patients, no differences in clinical outcome measures for olanzapine, risperidone, or quetiapine were found. The clinical efficacy and effectiveness of the atypical antipsychotics were not compared in clinical head-to-head trials in patients with major depressive disorder or behavioral disorders. Overall, insufficient evidence is available to determine the comparative effectiveness and efficacy of atypical antipsychotic use in major depressive or behavioral disorders.

Special Populations: No special populations based on age, gender, or comorbidities were identified.

Summary of the Comparative Clinical Evidence Published 1/2010-2/2016

Schizophrenia

A total of eleven systematic reviews & meta-analyses (SRs) and 27 comparative clinical trials (CCTs) published 2010-2016 were identified for evaluation in this report. All of the second-generation atypical antipsychotic agents are indicated in the treatment of schizophrenia. Of the 12 second-generation atypical antipsychotic agents, comparative clinical evidence is available for 11 of the agents, with the most clinical data available for risperidone and olanzapine: risperidone (9 SRs, 17 CCTs), olanzapine (11SRs, 10 CCTs), quetiapine (8 SRs, 8 CCTs), aripiprazole (8 SRs, 6 CCTs), clozapine (8 SRs, 3 CCTs), ziprasidone (7 SRs, 5 CCTs), paliperidone (2 SRs, 6 CCTs), lurasidone (1 SR, 4 CCTs), asenapine (1 SR, 1 CCT), iloperidone (1 SR), brexpiprazole (1 CCT) and no comparative clinical evidence available for cariprazine. A summary of this evidence can be found in the evidence tables available in the appendix of this document.

Risperidone. Nine systematic reviews & meta-analyses and 17 comparative clinical trials evaluating the comparative efficacy of risperidone in the treatment of schizophrenia are available for evaluation. A Cochrane review[278] of 45 randomized controlled trials (n = 7760 patients with schizophrenia) published in 2011 reported increased efficacy (reduced symptoms) with risperidone when compared to quetiapine and ziprasidone and reduced efficacy when compared to olanzapine. Discontinuation rate due to inefficacy was lower with risperidone when compared to ziprasidone but higher with risperidone when compared to olanzapine or clozapine. In general, risperidone therapy was associated with higher rates of extrapyramidal effects and increased prolactin levels and similar or reduced rates of metabolic effects and sedation when compared to the other second-generation antipsychotic agents.

Five additional Cochrane systematic reviews[279-283] evaluating the second-generation antipsychotic agents report increased efficacy with risperidone therapy when compared to quetiapine and ziprasidone; similar rates of efficacy when compared to aripiprazole, olanzapine and clozapine; and increased rates of extrapyramidal effects and prolactin levels when compared to most other second-generation agents. One large meta-analysis[284] of 212 randomized controlled trials (n = 43,049) published in 2013 reported safety and efficacy for 10 of the available second-generation antipsychotic agents (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, risperidone, quetiapine and ziprasidone). According to the evidence, risperidone was the third most effective agent after clozapine and olanzapine. Similar to the previous reports, risperidone was associated with higher rates of extrapyramidal effects and elevated prolactin levels when compared to the other antipsychotic agents.

Risperidone was compared to olanzapine in eight clinical trials. The majority of this evidence demonstrated similar rates of efficacy between the agents.[285-291] One randomized trial[292] of 244 patients with first-episode schizophrenia demonstrated significantly increased response rates in the olanzapine treatment groups when compared

to the risperidone treatment groups (p< 0.04). Oral risperidone was also compared to oral aripiprazole[288,293], oral quetiapine[288] and oral clozapine[294] and demonstrated similar rates of efficacy across all treatment groups. Of note, limited evidence suggests clozapine therapy is associated with increased rates of adherence when compared to risperidone therapy (based on a small trial of 30treatment naïve patients). One retrospective observational trial[295] comparing oral olanzapine to risperidone long-acting injection in 1622 patients with schizophrenia reported significantly increased response rates, increased treatment retention rates and reduced hospitalizations with injectable risperidone therapy compared to oral olanzapine therapy ($p < 0.05$ for all). Across the trials, risperidone therapy was associated with similar rates of adverse effects, including metabolic and extrapyramidal effects.

Risperidone long-acting injection was compared to oral quetiapine in a randomized, controlled trial[296] of 710 patients with schizophrenia. According to the evidence, risperidone injection was associated with a significantly longer time to relapse than oral quetiapine ($p = 0.0001$). Hyperprolactinemia occurred more frequently in the risperidone treatment group while sedation was reported more frequently in the quetiapine treatment group (p = NS for both). Risperidone long-acting injection was also compared to paliperidone palmitate injection in 5 clinical trials. The majority of this evidence demonstrated similar rates of efficacy between the agents.[297-300] One double-blind, randomized controlled trial[301] comparing flexible dosing of paliperidone palmitate monthly injection to risperidone long-acting biweekly injection in 749 acutely symptomatic schizophrenic patients failed to demonstrated noninferiority of paliperidone injection compared to risperidone injection. No significant differences in adverse events were reported between treatment groups across all the trials although there was a trend towards increased overall adverse event rate with paliperidone compared to risperidone. Paliperidone palmitate injection was compared to oral risperidone in a randomized, controlled trial[289] of 764 patients with schizophrenia. According to the evidence from this trial, efficacy and safety were the same between treatment groups with paliperidone injection exhibiting an increased time to relapse ($p = 0.019$).

Olanzapine. Eleven systematic reviews & meta-analyses and ten comparative clinical trials evaluating the comparative efficacy of olanzapine in the treatment of schizophrenia are available for evaluation. A Cochrane review[282] of 50 randomized controlled trials (n = 9476 patients with schizophrenia) published in 2010 reported increased efficacy (reduced symptoms) with olanzapine when compared to aripiprazole, quetiapine and ziprasidone; reduced rates of discontinuation due to lack of efficacy with olanzapine when compared to quetiapine, risperidone and ziprasidone; and reduced re-hospitalization rates with olanzapine when compared to quetiapine or ziprasidone. Olanzapine was associated with higher rates of metabolic effects, particularly weight gain when compared to the other second-generation antipsychotic agents. Six additional Cochrane systematic reviews[116,278-281,283] evaluating the second-generation antipsychotic agents report similar evidence with olanzapine demonstrating increased rates of efficacy when compared to quetiapine, ziprasidone and risperidone, similar rates of efficacy when compared to clozapine and aripiprazole; and increased rates of metabolic effects when compared to most other second-generation agents. A large meta-analysis[284] of 212 randomized

controlled trials (n = 43,049) reported olanzapine as the second most effective agent after clozapine. Similar to the previous reports, olanzapine was the antipsychotic agent with the highest rates of weight gain. In this analysis, olanzapine was associated with the lowest rate of all cause discontinuation when compared to all other antipsychotic agents. One meta-analysis[302] of 7 randomized controlled trials (n = 648) published in 2013 evaluated the efficacy of olanzapine and clozapine in patients with treatment-resistant schizophrenia. According to the evidence, clozapine was more effective than olanzapine in this patient population.

Olanzapine was compared to risperidone in eight clinical trials. As mentioned above, the majority of this evidence demonstrated similar rates of efficacy between the agents (see risperidone clinical efficacy section).[285-291] Olanzapine was also compared to aripiprazole and quetiapine in a randomized, controlled trial[288] of 332 adult patients with psychosis associated with schizophrenia or related disorder. According to the evidence, quetiapine was associated with increased rates of serious adverse events while olanzapine was associated with increased rates of non-serious adverse events. No differences in efficacy were reported between the treatment groups. A trial[303] comparing the long-term efficacy of olanzapine with asenapine in 502 patients with schizophrenia reported increased rates of efficacy (reduced symptoms at 52 weeks) with asenapine when compared to olanzapine ($p < 0.05$). However, treatment-related adverse events were higher in the asenapine treatment group when compared to the olanzapine treatment group. Oral olanzapine was also compared to paliperidone palmitate injection in a randomized, controlled trial[289] of 764 patients with schizophrenia. According to the evidence from this trial, efficacy and safety were the same between treatment groups with paliperidone injection exhibiting an increased time to relapse ($p = 0.019$).

Quetiapine. Eight systematic reviews & meta-analyses and eight comparative clinical trials evaluating the comparative efficacy of quetiapine in the treatment of schizophrenia are available for evaluation. A Cochrane review[280] of 35 randomized controlled trials (n = 5971 patients with schizophrenia) published in 2013 reported increased efficacy (reduced symptoms) with risperidone and olanzapine when compared to quetiapine; a discontinuation rate of over 50% with quetiapine therapy; and an overall reduced rate of extrapyramidal effects when compared to the other second generation antipsychotic agents. According to the evidence, quetiapine therapy was associated with fewer metabolic effects when compared to olanzapine or paliperidone and increased metabolic effects when compared to risperidone or ziprasidone. Six additional Cochrane systematic reviews[116,278,279,281-283] evaluating the second-generation antipsychotic agents report similar evidence with quetiapine demonstrating reduced efficacy when compared to risperidone and olanzapine. A large meta-analysis[284] of 212 randomized controlled trials (n = 43,049) reported comparable rates of efficacy and increased rates of sedation when compared to the other second-generation agents.

Quetiapine was compared to lurasidone in three clinical trials. Two[304,305] of the three trials reported no difference in safety, symptom reduction or relapse between the agents. Harvey et al[306] evaluated the efficacy of lurasidone 40-160 mg daily and quetiapine ER 200-800 mg daily in 267 patients with schizophrenia for up to 6 months.

At the end of the study period, lurasidone demonstrated significantly improved rates of cognitive performance compared to quetiapine ($p < 0.05$). One randomized, flexible-dose, clinical trial comparing quetiapine to aripiprazole and ziprasidone at 3 months and again at 1 year is available for evaluation.[307,308] A total 202 patients with first-episode schizophrenia received treatment with one of the three agents. At both three months and one year, discontinuation rates due to inefficacy were lowest with aripiprazole and ziprasidone and highest with quetiapine. Discontinuation rates due to adverse effects were greatest with ziprasidone and lowest with aripiprazole. No other differences were reported between treatment groups.

Risperidone long-acting injection was compared to oral quetiapine in a randomized, controlled trial[296] of 710 patients with schizophrenia. According to the evidence, risperidone injection was associated with a significantly longer time to relapse than oral quetiapine ($p = 0.0001$). Hyperprolactinemia occurred more frequently in the risperidone treatment group while sedation was reported more frequently in the quetiapine treatment group ($p = NS$). Paliperidone palmitate injection was also compared to oral quetiapine in a randomized, controlled trial of 764 patients with schizophrenia.[289] According to the evidence, efficacy and safety were the same between treatment groups with paliperidone injection exhibiting an increased time to relapse ($p = 0.19$). Oral quetiapine was also compared to oral aripiprazole, olanzapine and risperidone in a randomized, controlled trial[288] of 332 adult patients with psychosis associated with schizophrenia or related disorder. According to the evidence, quetiapine was associated with increased rates of serious adverse events while olanzapine was associated with increased rates of non-serious adverse events. No differences in efficacy were reported between the treatment groups.

Aripiprazole. Eight systematic reviews & meta-analyses and six comparative clinical trials evaluating the comparative efficacy of aripiprazole in the treatment of schizophrenia are available for evaluation. A Cochrane review[281] of 12 randomized controlled trials ($n = 6389$ patients with schizophrenia) published in 2013 reported similar rates of efficacy with aripiprazole when compared to risperidone or olanzapine and increased rates of efficacy when compared to ziprasidone. Overall, aripiprazole therapy was associated with the highest rate of patient preference when compared to the other second-generation agents with reduced rates of metabolic effects, sleepiness and shaking compared to the other agents. Four additional Cochrane systematic reviews[116,280,282] evaluating the second-generation antipsychotic agents report similar evidence with aripiprazole demonstrating similar to reduced rates of efficacy when compared to olanzapine and a generally lower incidence of adverse effects. A large meta-analysis[284] of 212 randomized controlled trials ($n = 43,049$) reported comparable rates of efficacy and reduced rates of adverse effects when compared to the other second-generation agents.

Aripiprazole was compared to brexpiprazole in the only comparative trial available evaluating the efficacy of brexpiprazole. Citrome et al[309] evaluated the efficacy of the agents in 97 patients with acute schizophrenia in a randomized, flexible-dosing trial. At 6 weeks no differences in efficacy (reduced symptoms) or safety were reported

between the treatment groups. One randomized, flexible-dose, clinical trial comparing aripiprazole to quetiapine and ziprasidone at 3 months and again at 1 year is available for evaluation.[307,308] A review of this trial is provided in the quetiapine clinical efficacy section. In summary, discontinuation rates due to inefficacy were highest with quetiapine and discontinuation rates due to adverse effects were greatest with ziprasidone. A trial comparing aripiprazole to quetiapine, olanzapine and risperidone[288] in 332 adult patients reported reduced rates of serious and non-serious adverse events with aripiprazole. No differences in efficacy were reported between treatment groups in either of the previous clinical trials. Aripiprazole was compared to risperidone in a second randomized, controlled trial[293] of 279 patients with schizophrenia. Again no differences in efficacy were reported between treatment groups; however, risperidone was associated with increased rates of weight gain and hyperprolactinemia when compared to aripiprazole. Aripiprazole was compared to injectable paliperidone palmitate in a single clinical trial. Schreiner et al[289] evaluated the efficacy of the agents in 764 patients with a recent diagnosis of schizophrenia. No differences in safety or efficacy were reported between treatment groups with paliperidone injection exhibiting an increased time to relapse ($p = 0.19$).

Clozapine. Eight systematic reviews & meta-analyses and three comparative clinical trials evaluating the comparative efficacy of clozapine in the treatment of schizophrenia are available for evaluation. A Cochrane review[279] of 27 randomized controlled trials (n = 3099 patients with schizophrenia) published in 2010 reported trials evaluating clozapine inconsistently demonstrated improved efficacy (reduced symptoms) when compared to olanzapine, quetiapine, risperidone and ziprasidone. According to the evidence, discontinuation due to inefficacy was lower with clozapine therapy while discontinuation due to adverse effects was higher with clozapine therapy. Overall, clozapine therapy was associated with increased rates of decreased white blood cell count, hypersalivation, sedation, weight gain and seizure rate. Five additional Cochrane systematic reviews[278,280-283] evaluating the second-generation antipsychotic agents report similar evidence with clozapine demonstrating reduced rates of discontinuation due to inefficacy and increased rates of some adverse effects including seizure. One meta-analysis[302] of 7 randomized controlled trials (n = 648) published in 2013 evaluated the efficacy of olanzapine and clozapine in patients with treatment-resistant schizophrenia. According to the evidence, clozapine was more effective than olanzapine in this patient population.

Three comparative clinical trials evaluating the efficacy of clozapine were identified for evaluation. Li et al[102] evaluated the efficacy of ziprasidone compared to clozapine when 213 patients with schizophrenia and metabolic disorders were switched from clozapine therapy to ziprasidone therapy. At 24 weeks, clinical efficacy (reduced symptoms) and safety (reduced metabolic effects) were significantly improved with ziprasidone treatment compared to prior clozapine treatment ($p < 0.05$). Sanz-Fuentenebro et al[294] conducted a small, long-term clinical trial evaluating the efficacy of clozapine and risperidone in 30 treatment naïve patients with first-episode schizophrenia. At one year, adherence rates were higher with clozapine therapy but no differences in efficacy (reduced symptoms) were reported between treatment groups. Metabolic effects were increased compared to baseline but similar between the treatment groups. Schnell et

al[310] conducted a small, long-term clinical trial evaluating the efficacy of clozapine compared to ziprasidone in patients with schizophrenia and concurrent cannabis abuse. At 12 months, clozapine therapy was associated with increased rates of efficacy, reduced rates of adherence and increased rates of adverse effects. Cannabis use was reduced from baseline and similar across patient groups.

Ziprasidone. Seven systematic reviews & meta-analyses and five comparative clinical trials evaluating the comparative efficacy of ziprasidone in the treatment of schizophrenia are available for evaluation. A Cochrane review[283] of 9 randomized controlled trials (n = 3361 patients with schizophrenia) published in 2009 reported reduced rates of efficacy and tolerability with ziprasidone when compared to risperidone and olanzapine and reduced rates of metabolic effects when compared to olanzapine, quetiapine or risperidone. There was a high rate of medication discontinuation (~60%) across all the included trials, which may limit the reliability of these results. Five additional Cochrane systematic reviews[278-282] evaluating the second-generation antipsychotic agents report similar evidence with ziprasidone demonstrating reduced rates of efficacy when compared to risperidone and olanzapine and a general reduced rate of metabolic effects when compared to the other agents. The large meta-analysis[284] of 212 randomized controlled trials (n = 43,049) reported comparable rates of efficacy, reduced rates of weight gain, increased rates of QTc prolongation and an overall increased discontinuation rate when compared to the other second-generation antipsychotic agents.

Five comparative clinical trials evaluating the efficacy of ziprasidone were identified for evaluation. One randomized, flexible-dose, clinical trial comparing ziprasidone to aripiprazole and quetiapine at 3 months and again at 1 year is available for evaluation.[307,308] A review of this trial is provided in the quetiapine clinical efficacy section. In summary, discontinuation rates due to inefficacy were highest with quetiapine and discontinuation rates due to adverse effects were greatest with ziprasidone. Two trials compared the efficacy of ziprasidone to clozapine. Li et al[102] evaluated the efficacy of ziprasidone in 213 patients with schizophrenia and metabolic disorders switched from clozapine therapy to ziprasidone therapy. At 24 weeks, clinical efficacy (reduced symptoms) and safety (reduced metabolic effects) were significantly improved with ziprasidone therapy compared to previous clozapine therapy ($p < 0.05$). Schnell et al[310] conducted a small, long-term clinical trial evaluating the efficacy of the agents in patients with schizophrenia and concurrent cannabis abuse. At 12 months, ziprasidone therapy was associated with increased rates of adherence, reduced rates of efficacy and lower rates of adverse effects compared to clozapine. Cannabis use was reduced from baseline and similar across patient groups. Potkin et al[311] evaluated the efficacy of ziprasidone compared to lurasidone in 301 adult outpatients with schizophrenia or related disorders. At 21 days, no differences in safety or efficacy were reported between treatment groups.

Paliperidone. Two systematic reviews & meta-analyses and six comparative clinical trials evaluating the comparative efficacy of paliperidone in the treatment of schizophrenia are available for evaluation. One Cochrane review[280] evaluating the efficacy of quetiapine compared to other second-generation agents reported paliperidone use is associated with increased rates of both metabolic effects and extrapyramidal effects

when compared to quetiapine. One large meta-analysis[284] of 212 randomized controlled trials (n = 43,049) published in 2013 reported safety and efficacy for 10 of the available second-generation antipsychotic agents (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, risperidone, quetiapine and ziprasidone). According to this evidence, paliperidone has comparable rates of efficacy and reduced rates of QTc prolongation and sedation when compared to the other agents.

Paliperidone palmitate was compared to risperidone long-acting injection in 5 clinical trials and oral risperidone in one clinical trial. A review of this evidence is provided in the risperidone clinical efficacy section. In summary, the majority of this evidence demonstrated similar rates of efficacy between the agents.[297-300] One trial[301] failed to demonstrated noninferiority of paliperidone injection compared to risperidone injection. No significant differences in adverse events were reported between treatment groups across all the trials although there was a trend towards increased overall adverse event rate with paliperidone compared to risperidone. When compared to oral risperidone (and a number of other oral antipsychotic agents including aripiprazole, haloperidol, olanzapine, paliperidone, quetiapine), paliperidone injection was associated with an increased time to relapse ($p = 0.019$).[289]

Lurasidone. One meta-analysis and four comparative clinical trials evaluating the comparative efficacy of lurasidone in the treatment of schizophrenia are available for evaluation. The meta-analysis[284] evaluating 212 randomized controlled trials (n = 43,049) reported safety and efficacy for 10 of the available second-generation antipsychotic agents (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, risperidone, quetiapine and ziprasidone). According to the evidence, lurasidone therapy is associated with reduced rates of efficacy, the highest rate of all-cause discontinuation, the highest rate of extrapyramidal adverse effects and the lowest rate of QTc prolongation compared to the other agents.

Lurasidone was compared to quetiapine in three clinical trials. Two[304,305] of the three trials reported no difference in safety, symptom reduction or relapse between the agents. Harvey et al[306] evaluated the efficacy of lurasidone and quetiapine in 267 patients with schizophrenia for up to 6 months. At the end of the study period, lurasidone demonstrated significantly improved rates of cognitive performance compared to quetiapine ($p < 0.05$). Potkin et al[311] evaluated the efficacy of lurasidone compared to ziprasidone in 301 adult outpatients with schizophrenia or related disorders. At 21 days, no differences in safety or efficacy were reported between treatment groups.

Asenapine. One meta-analysis and one comparative clinical trial evaluating the efficacy of asenapine in the treatment of schizophrenia are available for evaluation. The meta-analysis[284] evaluating 212 randomized controlled trials (n = 43,049) reported safety and efficacy for 10 of the available second-generation antipsychotic agents (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, risperidone, quetiapine and ziprasidone). According to the evidence, asenapine therapy is associated with reduced rates of efficacy and moderate rates of adverse effects compared to the other

agents. A comparative clinical trial[303] compared the long-term efficacy of olanzapine with asenapine in 502 patients with schizophrenia. According to the evidence, increased rates of efficacy (reduced symptoms at 52 weeks) were demonstrated with asenapine therapy when compared to olanzapine therapy ($p < 0.05$). However, treatment-related adverse events were higher in the asenapine treatment group when compared to the olanzapine treatment group (no p-value).

Iloperidone. One meta-analysis evaluating the efficacy of iloperidone in the treatment of schizophrenia is available for evaluation. The meta-analysis[284] evaluating 212 randomized controlled trials (n = 43,049) reported safety and efficacy for 10 of the available second-generation antipsychotic agents (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, risperidone, quetiapine and ziprasidone). According to the evidence, iloperidone therapy is associated with the lowest rate of efficacy; increased rates of all-cause discontinuation, weight gain and QTc prolongation; and reduced rates of sedation compared to the other agents.

Brexpiprazole. One comparative clinical trial evaluating the efficacy of brexpiprazole in the treatment of schizophrenia is available for evaluation. Citrome et al[309] evaluated the efficacy of brexpiprazole and aripiprazole in 97 patients with acute schizophrenia in a randomized, flexible-dosing trial. At 6 weeks, improvements were demonstrated compared to baseline but no differences in efficacy (reduced symptoms) or safety were reported between the treatment groups.

Special Populations. One Cochrane systematic review[312] of 13 randomized controlled trials (n = 1112) evaluated the efficacy of the first-generation and second-generation agents in the treatment of schizophrenia in adolescent patients aged 13-18 years. According to the evidence, first-generation agents demonstrate similar rates of efficacy as the second-generation agents and, as a class, the second-generation agents all demonstrated similar rates of efficacy. Overall, adverse event rate was higher with the first-generation agents compared to the second-generation agents and weight gain was reported more frequently in patients receiving clozapine, olanzapine and risperidone compared to aripiprazole. A second meta-analysis[313] of 3 randomized controlled trials (n = 666) evaluated the efficacy of aripiprazole, olanzapine and risperidone in adolescents with schizophrenia. According to the analysis, all three agents demonstrated efficacy compared to placebo with no differences in efficacy between treatment groups. The antipsychotic agents appear to be safe and effective in patients aged 13-18 years old. Additional clinical evidence is available for the switching from one antipsychotic agent to another, either due to adverse effects or inadequate symptom relief. In general, this clinical data does not demonstrate improvements in efficacy with therapeutic switching but does demonstrate improvements in the rate of adverse effects.[81,105,116,235,314] This may be helpful in specific populations, particularly the elderly in an attempt to reduce anticholinergic adverse effects.

<u>Bipolar Disorder</u>

A total of five systematic reviews & meta-analyses and two comparative clinical trials published 2010-2016 were identified for evaluation in this report. Eight of the second-generation atypical antipsychotic agents are indicated in the treatment of bipolar disorder: aripiprazole, asenapine, cariprazone, lurasidone, olanzapine, quetiapine, risperidone and ziprasidone. Clinical evidence for all of the above agents but cariprazone is included in this review; no comparative clinical evidence is available for cariprazone. A summary of the available evidence can be found in the evidence tables available in the appendix of this document.

Cipriani et al[315] conducted a large meta-analysis of 68 randomized, controlled trials (n = 16,073) evaluating the efficacy of all treatments (mood stabilizers, anticonvulsants, antipsychotics) in the treatment of bipolar mania in adults. According to the analysis, the antipsychotic agents are more effective than the other drug classes in reducing symptoms. Risperidone and olanzapine demonstrated the highest rates of efficacy compared to ziprasidone. Agents with the highest rating of acceptability included: risperidone, olanzapine, quetiapine and valproate. Cruz et al[316] conducted a meta-analysis of 5 randomized controlled trials evaluating the efficacy of the second-generation antipsychotic agents in the treatment of acute mania in adult patients. A reduction in symptoms was demonstrated with olanzapine and quetiapine compared to placebo. No differences in efficacy were reported for aripiprazole compared to placebo. Muralidharan et al[317] conducted a meta-analysis of 9 randomized, controlled trials (n = 1289) evaluating the efficacy of the second-generation antipsychotics in the treatment of mixed-episode bipolar disease in adults. According to the analysis, the second-generation agents are more effective than placebo but no differences between the agents were reported. Taylor et al[318] conducted a meta-analysis of 29 randomized controlled trials (n = 8331) evaluating the efficacy of the second-generation antipsychotics in the treatment of bipolar disorder in adults. According to the analysis, olanzapine and olanzapine-fluoxetine are more effective than the other second-generation agents. Vieta et al[319] conducted a systematic review of 19 randomized controlled trials evaluating the efficacy of mood stabilizers, antidepressants and antipsychotic agents in the treatment of bipolar disorder. According to the review, olanzapine and olanzapine-fluoxetine are more effective than the other agents. Aripiprazole, lamotrigine, lithium and paroxetine were not found to be more effective than placebo.

Two clinical trials further evaluating the efficacy of olanzapine were identified for evaluation. Berwaerts et al[320] evaluated the efficacy of oral paliperidone (3-12 mg/day) and olanzapine (5-20 mg/day) in 766 patients with bipolar I disorder. The primary outcome was median time to recurrence of the disorder; recurrence occurred at ~283 days in the placebo treatment group, at ~558 days in the paliperidone treatment group and did not occur at any time point in the olanzapine treatment group. Treatment-related adverse event rate was 64% in the olanzapine group, 55% in the paliperidone group and 59% in the placebo group. Mcintyre et al[321] evaluated the efficacy of asenapine and olanzapine in 308 adult patients with bipolar I disorder. At 40 weeks, treatment with asenapine and olanzapine demonstrated increased rates of symptom reduction compared to placebo but no differences in efficacy were reported between treatment groups. Treatment-related adverse event rate was 79.4% in the olanzapine treatment group, 86.1% in the asenapine

treatment group and 71.9% in the placebo group. Limited evidence based on this trial and other available evidence suggests asenapine may be a cost-effective alternative to olanzapine in patients with bipolar I disorder.[206,207]

Major Depressive Disorder

A total of three systematic reviews & meta-analyses published 2010-2016 were identified for evaluation in this report. Three of the second-generation atypical antipsychotic agents are indicated in the treatment of depressive disorder: aripiprazole, brexpiprazole and quetiapine. No comparative clinical evidence is available for brexpiprazole in the treatment of depression. A summary of the available evidence can be found in the evidence tables available in the appendix of this document.

One Cochrane review[322] evaluating the efficacy of the second-generation antipsychotic agents in the treatment of major depressive disorder is available. A total of 28 randomized, controlled trials (n = 8487) were included in the analysis. Symptom improvement occurred most frequently with quetiapine monotherapy and with augmentation with aripiprazole, quetiapine or olanzapine. Overall, the second-generation antipsychotic agents were associated with reduced tolerability due to increased rates of sedation, weight gain or laboratory abnormalities (hyperprolactinemia). Chen et al[62] provided an analysis of 12 randomized controlled trials evaluating the efficacy of the second-generation antipsychotic agents (quetiapine, aripiprazole, olanzapine, risperidone) in the treatment of non-psychotic major depression in adult patients. According to the evidence, the second-generation agents are more effective than placebo when used as monotherapy or adjunctive therapy in the treatment of depression. Adverse events were higher with the antipsychotic agents compared to placebo and appeared to be dose-related. Wen et al[323] conducted a meta-analysis of 17 randomized, controlled trials (n = 3807) evaluating the efficacy of the atypical antipsychotic agents as adjunctive treatment to antidepressant therapy in patients with major depressive disorder. According to the analysis, augmentation with an antipsychotic agent improves symptoms with increased discontinuation rates due to adverse effects.

Autistic Disorder

A total of one systematic review and two comparative clinical trials published 2010-2016 were identified for evaluation in this report. Two of the second-generation atypical antipsychotic agents are indicated in the treatment of autism spectrum disorders: aripiprazole and risperidone. A summary of the available evidence can be found in the evidence tables available in the appendix of this document. One systematic review[324] of 18 randomized controlled trials evaluated the efficacy of aripiprazole and risperidone, selective serotonin-reuptake inhibitors (SSRIs) and stimulants in the treatment of autism in children < 12 years old. According to the analysis, both aripiprazole and risperidone are more effective than SSRIs and stimulants. Ghanizadeh et al[325] compared the efficacy of aripiprazole and risperidone in the treatment of 59 pediatric patients with autism spectrum disorders. At 2 months, both aripiprazole and risperidone improved symptoms

compared to baseline. No differences in safety or efficacy were reported between the agents. Ishitobi et al[326] evaluated the efficacy of aripiprazole after pediatric patients with autism were switched from risperidone to aripiprazole therapy. At 12 weeks, no differences in efficacy were reported but a significantly decreased prolactin level was reported with aripiprazole therapy compared to risperidone therapy.

Tourette Disorder

One comparative clinical trial published 2010-2016 was identified for evaluation in this report. One of the second-generation atypical antipsychotic agents is indicated in the treatment of Tourette's disorder: aripiprazole. A summary of the available evidence can be found in the evidence tables available in the appendix of this document. Ghanizadeh et al[327] compared the efficacy of aripiprazole and risperidone in the treatment of 60 pediatric patients with tic disorder. At 2 months, both aripiprazole and risperidone improved symptoms compared to baseline. No differences in safety or efficacy were reported between the agents.

Safety

The most common adverse effects reported with the second-generation atypical antipsychotic agents include extrapyramidal symptoms (EPS), anticholinergic side effects, sedation, cardiovascular effects and metabolic effects. EPS is a broad term used to describe several movement disorders including acute dystonia, parkinsonism, akathisia and tardive dyskinesia. Acute dystonia, parkinsonism and akathisia typically develop during the initiation of treatment, while tardive dyskinesia can occur after several years of treatment. Anticholinergic effects including xerostomia, constipation, urinary retention, blurred vision and dry eyes are reported with most atypical antipsychotics. Sedation, somnolence, fatigue and lethargy are also reported with the atypical antipsychotic agents. Cardiovascular effects reported with the atypical antipsychotic agents include orthostatic hypotension, tachycardia and electrocardiogram (ECG) changes, including QTc prolongation. The most common metabolic effects reported with atypical antipsychotic agents are hyperprolactinemia, weight gain, hyperglycemia, development of diabetes mellitus and dyslipidemias. Adverse effects are usually dose dependent, and most are reversible after the medication is discontinued. Typical treatment of these adverse effects is either dose reduction or switching agents to find one with less unacceptable side effects. Serious adverse effects reported with atypical antipsychotic treatment include neuroleptic malignant syndrome (NMS), seizures, agranulocytosis, venous thromboembolism and suicidal behavior. Though most of these occur with an incidence of < 1%, they can be fatal if not managed immediately.

Cardiovascular toxicity, for example, is a rare but serious adverse effect which is reported with the antipsychotic agents. One systematic review[184] of case reports and case series describing overdose of aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone found 13 pediatric cases, 22 adolescent cases and 185 adult cases of toxicity. According to the report, none of the pediatric cases resulted in cardiovascular death. Many reports of QTc prolongation and hypotension, were reported in the adult and adolescent cases; however, only 3 deaths were reported and may have been due to direct cardiovascular toxicity. Overall, the evidence suggests overdoses of antipsychotic agents are unlikely to result in significant cardiovascular toxicity. A large observational trial evaluated the risk of QTc prolongation with ziprasidone, an antipsychotic agent know to prolong the QTc. According to the report, ziprasidone therapy was not associated with increased risk of nonsuicidal mortality in real-world use.[328]

One meta-analysis[205] of 28 randomized controlled trials evaluated the metabolic effects of the second-generation antipsychotic agents (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, zotepine). According to the review, both olanzapine and clozapine were associated with increased rates of weight gain compared to all other second-generation antipsychotics, In addition, olanzapine and clozapine were associated with increased glucose intolerance. Olanzapine was associated with increased rates of hypercholesterolemia compared to aripiprazole, risperidone and ziprasidone. Quetiapine was associated with increased rates of hypercholesterolemia compared to risperidone and ziprasidone. Some evidence suggests these metabolic effects may be dose-related.[183] A second systematic review[161] and meta-analysis evaluating the metabolic effects in pediatric patients is also available. According to the report, a statistically significant weight gain was reported with

aripiprazole, olanzapine and risperidone. However, more weight was gained with olanzapine therapy and a less significant amount of weight was gained with aripiprazole therapy.

As evidenced by the available comparative clinical evidence, differences in adverse events between the second-generation atypical antipsychotic agents are reported in the literature and are not always consistent. A recent review of the safety of the agents reported increased rates of EPS with risperidone and paliperidone, while iloperidone and quetiapine may be associated with lower incidence of EPS. According to the report, sedation is reported more frequently with clozapine and quetiapine and less frequently with aripiprazole, iloperidone, paliperidone, risperidone and ziprasidone. The agents with the highest rate of QTc prolongation include ziprasidone, quetiapine and risperidone, while lower rates are reported with lurasidone. Metabolic effects, including weight gain, dyslipidemia and diabetes, are reported more frequently with clozapine and olanzapine. Clozapine is also associated with increased rate of agranulocytosis, which limits its use. Differences in binding affinity between the antipsychotic agents for each dopamine tract result in differences in adverse effects. See table 7 in the pharmacology section of this report for an overview of the differences in affinities and subsequent differences in adverse events between the agents. Table 8 provides a summary of the safety data associated with the agents and Table 9 provides a review of the adverse events reported with the agents, based on package labeling.

Table 8. Warnings and Precautions for the Second-Generation Antipsychotic Agents[1,2]

	US Boxed Warnings	Warnings/Precautions	Other Considerations
Aripiprazole (Abilify®; others)	Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. Aripiprazole is not approved for the treatment of dementia-related psychosis	Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Elderly patients have an increased risk of adverse response to side effects or adverse reactions to antipsychotics Adverse events have been observed in animal reproduction studies. Aripiprazole crosses the placenta and is excreted in breast milk	Lactose: Tablets may contain lactose; avoid use in patients with galactose intolerance or glucose-galactose malabsorption Phenylalanine: Orally disintegrating tablets may contain phenylalanine Product interchangeability: Injection: There are two formulations available for intramuscular administration: Abilify is an immediate-release short-acting formulation and Abilify Maintena is an extended-release formulation. These products are not interchangeable
Asenapine (Saphris®)	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death	Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Pharmacokinetic studies showed a decrease in clearance in older adults (65 to 85 years of age) with psychosis compared to younger adults; increased risk of adverse effects and orthostasis may occur Use is **contraindicated** in patients with severe hepatic impairment	Phenylalanine: Orally disintegrating tablets may contain phenylalanine
Brexpiprazole (Rexulti®)	Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (≤24 years of age); Closely monitor patients for clinical worsening and suicidality particularly during the initial 1 to 2 months of therapy or during periods of dosage adjustments Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo	Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Adverse events were observed in some animal reproduction studies; It is not known if brexpiprazole is excreted in breast milk	Safety and efficacy have not been established in pediatric patients Brexpiprazole is not approved for the treatment of dementia-related psychosis Lactose: Tablets may contain lactose; avoid use in patients with galactose intolerance or glucose-galactose malabsorption
Cariprazine (Vraylar®)	Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo	Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Monitor carefully in the geriatric population	Pharmacokinetics: Plasma levels of cariprazine and its major metabolites accumulate over time; Adverse reactions may not appear until several weeks after initiation of treatment; Monitor response and for adverse reactions several weeks after the patient has begun treatment and after each dose increase

	US Boxed Warnings	Warnings/Precautions	Other Considerations
Clozapine (Clozaril®; others)	Clozapine treatment has caused severe neutropenia Orthostatic hypotension, bradycardia, syncope, and cardiac arrest have occurred with treatment Seizures have occurred with treatment; The risk is dose-related; Initiate treatment at 12.5 mg, titrate gradually, and use divided dosing Fatal myocarditis and cardiomyopathy have occurred with treatment Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death	Sialorrhea and drooling may occur with clozapine use; symptoms may be more profound during sleep and may be dose-related Use with caution in patients with hepatic disease or impairment; monitor hepatic function regularly Use with caution in patients with renal impairment; Dosage reduction may be necessary in patients with significant renal impairment Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy The elderly are more susceptible to adverse effects (including agranulocytosis, cardiovascular, anticholinergic, and tardive dyskinesia) Clozapine crosses the placenta and can be detected in the fetal blood and amniotic fluid; Clozapine was found to accumulate in breast milk in concentrations higher than the maternal plasma	Clozapine levels may be lower in patients who smoke; Smokers may require twice the daily dose as nonsmokers in order to obtain an equivalent clozapine concentration Medication should not be stopped abruptly; taper off over 1 to 2 weeks Brand/generic: Use caution when converting from brand to generic formulation; poor tolerability, including relapse, has been reported usually soon after product switch (1 to 3 months); monitor closely during this time Phenylalanine: FazaClo oral disintegrating tablets contain phenylalanine
Iloperidone (Fanapt®)	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death	Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Adverse events were observed in animal reproduction studies Use is not recommended in patients with severe hepatic impairment	
Lurasidone (Latuda®)	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies	Use with caution in patients with hepatic disease or impairment; dosage reduction is recommended in moderate-to-severe impairment Use with caution in patients with renal disease; dosage reduction is recommended in	Concomitant use with strong CYP3A4 inhibitors (eg, ketoconazole) and inducers (eg, rifampin) is **contraindicated**

	US Boxed Warnings	Warnings/Precautions	Other Considerations
		moderate-to-severe impairment Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy	
Olanzapine (Zyprexa®; others)	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death Adverse reactions with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of olanzapine extended release (ER); Olanzapine ER must be administered in a registered health care facility with ready access to emergency response services	Use with caution in patients with hepatic disease or impairment; may increase transaminases (primarily ALT) Use with caution in patients with renal disease Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Elderly patients have an increased risk of adverse side effects or adverse reactions to antipsychotics Adverse events were observed in animal reproduction studies; Olanzapine crosses the placenta and can be detected in cord blood at birth and Olanzapine is excreted into breast milk	Use in patients ≥13 years of age may result in increased weight gain and sedation, as well as greater increases in LDL cholesterol, total cholesterol, triglycerides, prolactin, and liver transaminase levels when compared with adults; Adolescent patients should be maintained on the lowest dose necessary Olanzapine levels may be lower in patients who smoke; Smokers may require a daily dose 30% higher than nonsmokers in order to obtain an equivalent olanzapine concentration Zyprexa Relprevv is only available under a restricted distribution program Polysorbate 80: Some dosage forms may contain polysorbate 80 (also known as Tweens); Hypersensitivity reactions, usually a delayed reaction, have been reported following exposure to pharmaceutical products containing polysorbate 80 in certain individuals
Paliperidone (Invega®)	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death	Use with caution in patients with mild renal disease; dosage reduction is recommended; Not recommended in patients with moderate to severe impairment Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Paliperidone is excreted in breast milk	Extended-release tablet: Use is not recommended in patients with preexisting severe gastrointestinal narrowing disorders
Quetiapine (Seroquel®; others)	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death Antidepressants increased the risk of suicidal	Use with caution in patients with hepatic disease or impairment; may increase transaminases (primarily ALT; transient, reversible); Dose adjustment recommended	Quetiapine is not approved in the US for use in children <10 years of age Dose escalation should be performed with caution in elderly patients; consider slower

	US Boxed Warnings	Warnings/Precautions	Other Considerations
	thoughts and behavior in children, adolescents, and young adults in short-term studies	Use with caution in patients with renal disease; experience is limited Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Adverse events were observed in animal reproduction studies. Quetiapine crosses the placenta and can be detected in cord blood and Quetiapine is excreted into breast milk	rates of dose titration and lower target doses Withdrawal syndrome: Use caution when withdrawing therapy; decrease slowly and monitor for withdrawal symptoms
Risperidone (Risperdal®; others)	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death	Use with caution in patients with hepatic disease or impairment; dosage reduction is recommended Use with caution in patients with renal disease; dosage reduction is recommended Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy Adverse events were observed in animal reproduction studies. In human studies, risperidone and its metabolite cross the placenta and Risperidone and its metabolite are excreted in breast milk	Benzyl alcohol and derivatives: Some dosage forms may contain sodium benzoate/benzoic acid; benzoic acid (benzoate) is a metabolite of benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity Injectable suspension: Vehicle used (polylactide-co-glycolide microspheres) has rarely been associated with retinal artery occlusion in patients with abnormal arteriovenous anastomosis (eg, patent foramen ovale); Not for intravenous use; administer only as an intramuscular injection.
Ziprasidone (Geodon®)	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death **Contraindications**: History of (or current) prolonged QT; congenital long QT syndrome; recent myocardial infarction; uncompensated heart failure; concurrent use of other QTc-prolonging agents including arsenic trioxide, chlorpromazine, class Ia antiarrhythmics, class III antiarrhythmics	Use with caution in patients with hepatic disease or impairment Use the intramuscular formulation with caution in patients with renal impairment Adverse events were observed in animal reproduction studies	Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy Intramuscular formulation: Use the intramuscular formulation with caution in patients with renal impairment; formulation contains cyclodextrin, an excipient which may accumulate in renal insufficiency, although the clinical significance of this finding is uncertain

Table 9. Adverse Events Reported with the Second-Generation Atypical Antipsychotic Agents[1,2]

Adverse Effect	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Cardiovascular												
Cardiorespiratory failure	+				+			+		+	+	
Cerebrovascular accident	+		+			+	+	+			+	
Hypertension										+++		
Hypotension			+	+	+++	++	+	++	+	++		++
Myocardial Infarction	+											
Peripheral edema								++				
Prolonged QT interval	+	+			+				+	+	+	+
Syncope			+		++		+		+	+	+	+
Tachycardia					+++	++			+++	++		
Transient Ischemic Attack	+		+	+								
Dermatologic												
Erythema multiforme					+							
Injection site reaction									+++			++
Rash											++	++
Stevens-Johnson syndrome					+							
Endocrine/Metabolic												
Diabetes mellitus				+	+			+				+
Diabetic ketoacidosis	+		+		+			+		+	+	
Hyperglycemia		++	++	+	+++	+		+++				+
Hyperprolactinemia						+++		+++	+++		++	+
Hypothermia											+	
Raised cholesterol		+	+++	+				+++		+++		
Sweating					++							
Weight gain	+++	+++	+++		+++	++		+++	+++	+++	+++	++
Gastrointestinal												
Abdominal pain										++	++	
Constipation	++				+++			++	++	++	+++	++
Diarrhea							++				++	++
Dysphagia									+			+

Adverse Effect	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Esophageal dysmotility				+								
Excessive salivation					+++						++	
Indigestion				++					++	++	++	++
Nausea	+++				+++		+++			++	++	++
Oral paresthesia		++										
Pancreatitis	+							+		+	+	
Peristalsis					+							
Vomiting	++			++			++			++	+++	++
Xerostomia					++	++		+++		+++	++	
Hematologic												
Agranulocytosis	+		+				+		+	+	+	
Bone marrow depression												+
Eosinophilia					+							
Leukopenia	+			+				+	+	+	+	
Neutropenia	+			+	+					+	+	
Thrombocytopenia					+						+	
Immunologic												
Anaphylaxis									+	+		
Hypersensitivity reaction		+						+				+
Neurologic												
Akathisia	+++	++	++	+++			+++	+++	+++		++	++
Asthenia								+++		++		++
Dizziness	++	++			+++	+++		+++		+++	+++	+++
Dyskinesia									++			
Dystonia								++	++		++	
Extrapyramidal sign	+++	++	++	+++			+++		+++	++		+++
Headache	+++		++		++					+++		+++
Insomnia	+++									++		
Lethargy	+++					++				++		
Neuroleptic Malignant Syndrome	+	+	+	+	+	+	+		+	+	+	+
Parkinsonism							+++		+++		+++	

Adverse Effect	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Sedation	+++				+++						++	
Seizure	+		+	+	++		+	+	+	+	+	+
Somnolence	+++	+++		++	+++	+++	+++	+++	+++	+++		+++
Tardive dyskinesia	+			+			+		+	+	++	+
Tremor	++				++			+++	++	++	++	++
Vertigo					+							
Ophthalmic												
Angle-closure glaucoma					+							
Blurred vision	++				++						++	++
Psychiatric												
Agitation									++	+++		
Anxiety	+++						++	++	++		+++	++
Restlessness	++			++								
Suicide risk	+	++	+	+			+	+		+		
Respiratory												
Cough											++	
Nasal congestion						++				++	++	
Nasopharyngitis									++	++	++	
Pulmonary embolism					+			+			+	
Respiratory tract infection					+						++	++

Key: +++ - >10%; ++ - 1-10%; + - <1%

Summary

The antipsychotic agents have been used for over 6 decades to treat psychosis associated with schizophrenia, bipolar mania, acute agitation and other mental health conditions. All of the second-generation atypical antipsychotics are labeled for the treatment of schizophrenia and some are also labeled for use in the treatment of bipolar disorder, depression, autism and Tourette's disorder. All of the agents are available in oral tablet or capsule formulations and many of the agents are available in orally disintegrating tablets, oral solutions and injectable formulations which may be helpful to improve compliance or patient preference. Clinical guidelines for the treatment of schizophrenia treatment with a single antipsychotic agent but do not recommend any of the agents over another. Treatment with more than one antipsychotic agent should be avoided and clozapine is recommended in treatment-resistant schizophrenia disease. Clinical guidelines for the treatment of bipolar disorder recommend medication therapy for acute mania episodes with mood stabilizers and select anticonvulsant or antipsychotic agents. Medication therapy should be continued until full remission is achieved and combination therapy is recommended in patients with continued treatment-resistance to a single agent. Clinical guidelines for the treatment of depression recommend use of a second-generation antidepressant for the treatment of depression; adjunctive treatment with another class of medications, including atypical antipsychotic agents, is recommended in patients who are treatment-resistant to antidepressant monotherapy.

Clinical experience with the second-generation atypical antipsychotic agents in treating patients with mental health disorders is extensive. The majority of comparative evidence evaluated in this report comes from the Oregon Report and 11 systematic review trials involving nearly 600 clinical trials and over 66,000 patients. Risperidone and olanzapine are included in most systematic reviews, meta-analyses and clinical trials evaluating the efficacy of the second-generation antipsychotic agents. Limited evidence is available for the new agents: brexpiprazole, cariprazine and iloperidone. In general, similar rates of efficacy were demonstrated across the available 12 second-generation antipsychotic agents in the treatment of schizophrenia, bipolar disorder and depressive disorder. Five patient populations may require special consideration when being treated with the second-generation atypical antipsychotic agents: geriatric patients, pediatric patients, patients with metabolic disease, patients with seizure disorders and patients with a drug and alcohol abuse disorder. In general, these patients may require changes in dosing schedules, reductions in duration of therapy, judicious medication selections and frequent follow-ups.

The most common adverse effects reported with the second-generation atypical antipsychotic agents include extrapyramidal symptoms, anticholinergic side effects, sedation, cardiovascular effects and metabolic effects. Serious adverse effects reported with the agents include neuroleptic malignant syndrome, seizures, agranulocytosis, venous thromboembolism, cardiovascular arrhythmias and suicidal behavior. Differences in adverse events between the second-generation atypical antipsychotic agents are reported in the literature and are not always consistent. Differences in adverse event rates may be tied to pharmacological actions; differences in binding affinity between the antipsychotic agents for each of the dopamine tracts may result in differences in adverse effects. Careful attention should be paid to adverse effect profile for each individual agent when selecting an agent for treatment of mental health disorders.

Overall, the second-generation atypical antipsychotic agents are effective treatment options for mental health disorders. When compared in clinical trials, the agents demonstrate similar rates of efficacy with varying rates of adverse effects. The second-generation antipsychotic products are available in many dosage forms, varying potencies and differing durations of action. Treatment management must be individualized for each patient and include careful evaluation of patient history, age, comorbidities, type and severity of mental health disorder, underlying diseases and concurrent medications.

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Appendix: Evidence Tables

Evidence Table 1. Systematic Reviews Evaluating the Second-Generation Atypical Antipsychotic Agents

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Autism Spectrum Disorder					
Mcpheeters et al, 2011[324] Systematic review of 18 trials	18 trials	Children < 12 years of age with autism spectrum disorders	Antipsychotic medications (Aripiprazole, Risperidone; n = 9) Selective serotonin-reuptake inhibitors (SSRIs; n = 5) Stimulants (n = 4)	Symptom improvement • Aripiprazole = Risperidone > SSRIs, stimulants = Placebo	Not reported
Bipolar Disorder					
Cipriani et al, 2011[315] Meta-analysis of 68 randomized controlled trials	16073	Adults with acute mania	Aripiprazole Asenapine Carbamazepine Gabapentin Haloperidol Lamotrigine Lithium Olanzapine Quetiapine Risperidone Topiramate Valproate Ziprasidone	Reduced symptoms • Antipsychotic agents > all other agents • Risperidone = Olanzapine > Ziprasidone	Acceptability • Risperidone, Olanzapine, Quetiapine, Valproate > all other agents
Cruz et al, 2010[316] Meta-analysis of 5 randomized controlled trials (RCTs)	5 RCTs	Adult patients with bipolar disorder acute mania	Aripiprazole(n = 2) Olanzapine (n = 2) Quetiapine (n= 1) Quetiapine-Fluoxetine (n = 1)	Reduced symptoms* • Olanzapine > Placebo • Quetiapine > Placebo • Aripiprazole = Placebo *rapid onset of action linked to increased efficacy	Not reported

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Muralidharan et al, 2013[317,318] Meta-analysis of 9 randomized, controlled trials	1289	Adults with mixed episode bipolar disorder	Aripiprazole Asenapine Olanzapine Paliperidone ER Risperidone Ziprasidone	Reducing symptoms* • Antipsychotic agents > Placebo *increased efficacy in depression episodes compared to mania episodes	Not reported
Taylor et al, 2014[318] Meta-analysis of 29 randomized, controlled trials	8331	Adults with bipolar disorder	Aripiprazole Lurasidone Olanzapine Olanzapine-Fluoxetine Risperidone Ziprasidone	Effect size • Olanzapine = Olanzapine-Fluoxetine > others Switch to mania • Ziprasidone < Quetiapine < others Reduced symptoms • Olanzapine-Fluoxetine > Lurasidone > others	Not reported
Vieta et al, 2010[319] Systematic review of 19 randomized, controlled trials (RCTs)	19 RCTs	Patients with bipolar depression	Aripiprazole Divalproex Lamotrigine Lithium Olanzapine Olanzapine-Fluoxetine Paroxetine Phenelzine, Quetiapine	Reduced symptoms • Olanzapine-Fluoxetine, Quetiapine > Divalproex, Olanzapine, Phenelzine > Aripiprazole, Lamotrigine, Lithium, Paroxetine = Placebo Remission • All agents > Phenelzine, Aripiprazole, Lithium, Paroxetine = Placebo	Discontinuation rate • Olanzapine = Olanzapine-Fluoxetine > all other agents

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Depressive Disorder					
Chen et al, 2011[62] Analysis of 12 randomized controlled studies (RCTs)	12 RCTs	Adult patients with non-psychotic major depressive disorder	Second-generation Antipsychotics (SGAs): Quetiapine monotherapy Aripiprazole adjunctive therapy Olanzapine adjunctive therapy Quetiapine adjunctive therapy Risperidone adjunctive therapy	Reducing symptoms* • SGA monotherapy > Placebo • SGA adjunctive therapy > Placebo	Adverse effect discontinuation rate* • SGAs > Placebo *dose related
Komossa et al, 2010[322] Cochrane Systematic review of 28 randomized, controlled trials	8487	People with major depressive disorder or dysthymia	Amisulpride Aripiprazole Olanzapine Quetiapine Risperidone	Symptom improvement • Quetiapine monotherapy > Placebo • Aripiprazole, Quetiapine, Olanzapine augmentation > Placebo	Tolerability • All antipsychotic agents < antidepressants or other agents
Wen et al, 2014[323] Meta-analysis of 17 randomized, controlled trials	3807	Patients with major depressive disorder	Atypical Antipsychotic agents as adjunct to antidepressant therapy: Olanzapine Quetiapine Aripiprazole Risperidone	Symptom improvement • Antipsychotic augmentation > Placebo Remission rate • Antipsychotic augmentation > Placebo	Discontinuation rate due to adverse effects • Antipsychotic augmentation > Monotherapy

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Schizophrenia					
Asmal et al, 2013[280] Cochrane Systematic review of 35 randomized, controlled trials	5971	People with schizophrenia or schizophrenia-like psychoses	Quetiapine 50-800 mg/day versus Aripiprazole Clozapine Olanzapine Paliperidone Risperidone Ziprasidone	Reducing symptoms* • Risperidone ≥ Quetiapine • Olanzapine ≥ Quetiapine *most important limiting factor: Quetiapine discontinuation rate >50%	Metabolic effects (weight gain, diabetes) • Quetiapine < Olanzapine • Quetiapine < Paliperidone • Risperidone < Quetiapine • Ziprasidone < Quetiapine Parkinsonian effects • Quetiapine < Aripiprazole • Quetiapine < Olanzapine • Quetiapine < Paliperidone • Quetiapine < Risperidone • Quetiapine < Ziprasidone
Ardizzone et al, 2010[313] Meta-analysis of 3 randomized controlled trials	666	**Adolescents** with psychosis, ages 13-18 years	Aripiprazole Risperidone Olanzapine	Reducing symptoms • Aripiprazole = Risperidone = Olanzapine > Placebo	Weight gain • Olanzapine > Placebo Extrapyramidal adverse effects • Risperidone > Placebo • Aripiprazole, high dose > Placebo

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Asenjo Lobos et al, 2010[279] Cochrane Systematic review of 27 randomized, controlled trials	3099	People with schizophrenia or schizophrenia-like psychoses	Clozapine versus Olanzapine Quetiapine Risperidone Ziprasidone Zotepine	Reducing symptoms* • Clozapine = Olanzapine, Risperidone, Ziprasidone, Quetiapine Inefficacy discontinuation rate: • Clozapine < Risperidone *most important limiting factor: discontinuation ~30% across all agents	Adverse effect discontinuation rate • Clozapine > Olanzapine • Clozapine > Risperidone Extrapyramidal effects • Clozapine < Risperidone Decreased white blood cell count • Clozapine > Olanzapine Hypersalivation • Clozapine > Olanzapine, Risperidone, Quetiapine Sedation • Clozapine > Olanzapine, Risperidone, Quetiapine Seizure rate • Clozapine > Olanzapine, Risperidone Weight gain • Clozapine > Risperidone

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Khanna et al, 2013[281] Cochrane Systematic review of 12 randomized, controlled trials [update of Komossa et al, 2009]	6389	People with schizophrenia or schizophrenia-like psychoses	Aripiprazole Versus Amisulpride Clozapine Olanzapine Quetiapine Risperidone Sertindole Ziprasidone Zotepine	Reducing symptoms* • Aripiprazole = Risperidone • Aripiprazole = Olanzapine • Aripiprazole ≥ Ziprasidone *most important limiting factor: discontinuation ~30% across all agents	Metabolic effects (weight gain, cholesterol) • Aripiprazole < Risperidone • Aripiprazole < Olanzapine Sleepiness • Aripiprazole < Risperidone • Aripiprazole < Olanzapine Shaking • Aripiprazole < Risperidone • Aripiprazole < Olanzapine Patient Preference • Aripiprazole > all other agents
Komossa et al, 2009[283] Cochrane Systematic review of 9 randomized, controlled trials	3361	People with schizophrenia or schizophrenia-like psychoses	Ziprasidone versus Amisulpride Clozapine Olanzapine Quetiapine Risperidone	Reducing symptoms* • Risperidone > Ziprasidone • Olanzapine > Ziprasidone *most important limiting factor: discontinuation ~60% across all agents	Tolerability • Risperidone > Ziprasidone • Olanzapine > Ziprasidone • Ziprasidone = Clozapine Metabolic Effects (weight gain, cholesterol) • Ziprasidone < Olanzapine, Quetiapine, Risperidone Extrapyramidal Effects • Olanzapine < Ziprasidone < Risperidone Increased prolactin levels • Quetiapine < Ziprasidone < Risperidone

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Komossa et al, 2010[282] Cochrane Systematic review of 50 randomized, controlled trials	9476	People with schizophrenia or schizophrenia-like psychoses	Olanzapine Versus Amisulpride Aripiprazole Clozapine Quetiapine Risperidone Sertindole Ziprasidone Zotepine	Reducing symptoms • Olanzapine > Aripiprazole • Olanzapine > Quetiapine • Olanzapine > Ziprasidone Inefficacy discontinuation rate • Olanzapine < Quetiapine • Olanzapine < Risperidone • Olanzapine < Ziprasidone Re-hospitalization rate • Olanzapine < Quetiapine • Olanzapine < Ziprasidone	Weight Gain • Olanzapine > all other agents Metabolic effects (diabetes, cholesterol) • Olanzapine ≥ all other agents Extrapyramidal side effects • Olanzapine > Quetiapine • Risperidone > Olanzapine Increased prolactin levels • Olanzapine > Aripiprazole, Clozapine, Quetiapine • Risperidone > Olanzapine

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Komossa et al, 2011[278] Cochrane Systematic review of 45 randomized, controlled trials	7760	People with schizophrenia or schizophrenia-like psychoses	Risperidone Versus Amisulpride Aripiprazole Clozapine Olanzapine Quetiapine Sertindole Ziprasidone Zotepine	Reducing symptoms • Risperidone > Quetiapine • Risperidone > Ziprasidone • Olanzapine > Risperidone Inefficacy discontinuation rate • Risperidone < Ziprasidone • Olanzapine < Risperidone • Clozapine < Risperidone	Overall acceptability of treatment • Risperidone > Ziprasidone • Olanzapine > Risperidone Extrapyramidal side effects • Risperidone > all other agents Increased prolactin levels • Risperidone > all other agents Metabolic effects (weight gain, cholesterol) • Risperidone < Clozapine, Olanzapine, Quetiapine • Risperidone > Aripiprazole, Ziprasidone Sedation • Risperidone < Clozapine • Risperidone < Quetiapine Seizure rate • Risperidone < Clozapine •
Kumar et al, 2013[312] Cochrane Systematic review of 13 randomized, controlled trials	1112	**Adolescents** with psychosis, ages 13-18 years	All first-generation and second-generation antipsychotic agents	First-generation agents = Second-generation agents All second-generation agents demonstrated similar rates of efficacy	Adverse event rate First-generation agents $\geq$ Second-generation agents Weight Gain Aripiprazole < Clozapine, Olanzapine, Risperidone

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Leucht et al, 2013[284] Meta-analysis of 212 randomized, controlled trials	43049	Patients with schizophrenia or related disorders	Aripiprazole Asenapine Clozapine Iloperidone Lurasidone Olanzapine Paliperidone Risperidone Quetiapine Ziprasidone	Mean improvement in symptom reduction compared to placebo, CI • Clozapine 0·88, 0·73–1.03 • Olanzapine 0·59, 0·53–0·65 • Risperidone 0·56, 0·50–0·63 • Paliperidone 0·50, 0·39–0·60 • Quetiapine 0·44, 0·35–0·52 • Aripiprazole 0·43, 0·34–0·52 • Ziprasidone 0·39, 0·30–0·49 • Asenapine 0·38, 0·25–0·51 • Lurasidone 0·33, 0·21–0·45 • Iloperidone 0·33, 0·22–0·43	All Cause Discontinuation, Odds Ratio • Olanzapine 0·46 • Clozapine 0·46 • Paliperidone 0·48 • Risperidone 0·53 • Aripiprazole 0·61 • Quetiapine 0·61 • Asenapine 0·69 • Iloperidone 0·69 • Ziprasidone 0·72 • Lurasidone 0·77 Weight Gain, Standardized Mean • Ziprasidone 0·10 • Lurasidone 0·10 • Aripiprazole 0·17 • Amisulpride 0·20 • Asenapine 0·23 • Paliperidone 0·38 • Risperidone 0·42 • Quetiapine 0·43 • Iloperidone 0·62 • Clozapine 0·65 • Olanzapine 0·74 Extrapyramidal Side Effects, Odds Ratio • Clozapine 0·3 • Olanzapine 1·00 • Quetiapine 1·01 • Aripiprazole 1·20 • Iloperidone 1·58 • Ziprasidone 1·61 • Asenapine 1·66 • Paliperidone 1·81 • Risperidone 2·09 • Lurasidone 2·46 Increased Prolactin Levels, Standardized Mean • Aripiprazole –0·22 • Quetiapine –0·05 • Asenapine 0·12 • Olanzapine 0·14

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
					• Iloperidone 0·21 • Ziprasidone 0·25 • Lurasidone 0·34 • Risperidone 1·23 • Paliperidone 1·30 QTc Prolongation, Odds Ratio • Lurasidone –0·10 • Aripiprazole 0·01 • Paliperidone 0·05 • Quetiapine 0·17 • Olanzapine 0·22 • Risperidone 0·25 • Asenapine 0·30 • Iloperidone 0·34 • Ziprasidone 0·41 Sedation, Odds Ratio • Paliperidone 1·40 • Iloperidone 1·71 • Aripiprazole 1·84 • Lurasidone 2·45 • Risperidone 2·45 • Asenapine 3·28 • Olanzapine 3·34 • Quetiapine 3·76 • Ziprasidone 3·80 • Clozapine 8·82
Mukundan et al, 2010[116] Cochrane Systematic review of 4 randomized, controlled trials	636	Patients with schizophrenia receiving antipsychotic therapy	Olanzapine => Aripiprazole Olanzapine => Quetiapine	Change in symptom control • Olanzapine = Aripiprazole • Olanzapine = Quetiapine	Change in metabolic Effects (weight, bmi, blood glucose) • Olanzapine > Aripiprazole • Olanzapine > Quetiapine
Souza et al, 2013[302] Meta-analysis of 7 randomized, controlled trials	648	Patients with treatment-resistant schizophrenia	Olanzapine Clozapine	Reducing symptoms • Clozapine > Olanzapine	Not reported

Evidence Table 2. Clinical Trials Evaluating the Second-Generation Atypical Antipsychotic Agents

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Autism					
Ghanizadeh et al, 2014[325] Randomized, double-bling clinical trial	59	Children and adolescents with autism spectrum disorders	Aripiprazole Risperidone Duration: 2 months	Symptom improvement • Aripiprazole = Risperidone > Baseline	Adverse effect rate • Aripiprazole = Risperidone
Ishitobi et al, 2013[326] Prospective, open-label trial	9	Children and adolescents with autism spectrum disorders (ages 9-22)	Risperidone => Aripiprazole	Symptom improvement • Aripiprazole = Risperidone	Prolactin levels • Aripiprazole < Risperidone
Bipolar Disorder					
Berwaerts at al, 2012[320] Randomized, placebo- and active-controlled study	766	Patients with bipolar I disorder	Paliperidone ER (3–12 mg/day) Olanzapine(5–20 mg/day) Placebo	Median time to recurrence • Olanzapine: not observed • Paliperidone: 558 days • Placebo: 283 days	Treatment-emergent adverse events • Olanzapine: 64% • Paliperidone: 55% • Placebo: 59%
Mcintyre et al, 2010[329] Randomized, double-bling, flexible dose trial	308	Patients with bipolar I disorder.	Asenapine 5-10 mg twice daily Olanzapine 5–20 mg daily Placebo Duration: 40-weeks	Reduced symptoms • Asenapine = Olanzapine > Placebo	Treatment-emergent adverse events (most frequent) • Placebo: 71.9% (headache somnolence) • Asenapine: 86.1% (insomnia, sedation, depression) • Olanzapine: 79.4% (weight gain, somnolence, sedation)
Schizophrenia					

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Agid et al, 2011[292] Three prospective trials with a retrospective analysis	244	Individuals with first-episode schizophrenia or schizoaffectve disorder	Olanzapine Risperidone	Response rate Trial 1 • Olanzapine: 82.1% • Risperidone: 66.3%, p = 0.005 Trial 2 • Olanzapine: 25.7% • Risperidone: 4%, p = 0.04	Not reported
Ayesa-Arriola et al, 2013[285] Prospective, randomized, open-label study	79	Patients with first episode of schizophrenia spectrum disorders	Haloperidol (n=28) Olanzapine (n=23) Risperidone (n=28) Duration: 3 years	Cognitive Improvement • Olanzapine = Risperidone	Extrapyramidal side effects Olanzapine = Risperidone
Crespo-Facorro et al, 2012[286] Randomized, flexible-dose, open-label trial	174	Patients with first-episode schizophrenia-spectrum disorders	Haloperidol (n = 56) Olanzapine (n = 55) Risperidone (n = 63) Duration: 3 years	Symptom Improvement • Risperidone = Olanzapine Treatment discontinuation rate • Haloperidol > Risperidone, p < 0.005 • Haloperidol > Olanzapine, p < 0.005 Time to discontinuation • Olanzapine = 23.8 months • Risperidone = 20.7 months, p = 0.002	Somnolence • Quetiapine > Risperidone Amenorrhea • Risperidone > Olanzapine

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Crespo-Facorro et al, 2013[308] Randomized, flexible-dose, open-label trial	202	Patients with first-episode schizophrenia-spectrum disorders	Aripiprazole (n = 78) Ziprasidone (n = 62) Quetiapine (n = 62) Duration: 3 months	Treatment discontinuation rate: Efficacy* • Aripiprazole: 23.1% • Ziprasidone: 37.1% • Quetiapine: 61.3%, p < 0. 001 *Insufficient efficacy in the group of Quetiapine is the main reason for discontinuation rate differences	Treatment discontinuation rate: adverse effects • Aripiprazole: 6.4% • Ziprasidone: 12.9% • Quetiapine: 11.3%
Crespo-Facorro et al, 2014[307] Randomized, flexible-dose, open-label trial	202	Patients with first-episode schizophrenia-spectrum disorders	Aripiprazole (n = 78) Ziprasidone (n = 62) Quetiapine (n = 62) Duration: 1 year	Treatment discontinuation rate: Efficacy* • Aripiprazole: 43.6% • Ziprasidone: 66.1% • Quetiapine: 82.3%, p < 0. 001	Treatment discontinuation rate: adverse effects • Aripiprazole: 10.3% • Ziprasidone: 29% • Quetiapine: 11.3%, p = 0.005
Citrome et al, 2016[309] Randomized, open-label, flexible-dosing trial	97	Patients with acute schizophrenia	Aripiprazole 15 mg/day Brexpiprazole 3 mg/day Duration: 6-weeks	Reduced symptoms • Aripiprazole: -19.4 • Brexpiprazole: -22.9	Akathisia • Aripiprazole: 21.2% • Brexpiprazole: 9.4%
Finding et al, 2010[287] Randomized, double-blind extension phase that followed an 8-week, double-blind acute trial[330,331]	54/116	Patients (age 8–19 years) who improved during acute trial were eligible to continue on the same medication for up to 44 additional weeks	Molindone (n = 20) Olanzapine (n = 13) Risperidone (n = 21) Duration: 44 weeks	Symptom improvement • Olanzapine = Risperidone Treatment discontinuation rate* • Olanzapine = Risperidone *only 12% continued their treatment for the full 52-weeks	Elevated Prolactin Levels • Risperidone > Olanzapine Metabolic Effects* • Risperidone = Olanzapine *greater with olanzapine in the acute phase

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Fleischhacker et al, 2012[301] Phase-III, double-blind, randomized, coltrolled trial	749	Acutely symptomatic schizophrenia patients	Paliperidone palmitate injection on days 1 and 8, and flexible dosing 25–100 mg (39–156 mg) once-monthly Risperidone long-acting injectable 25 mg on days 8 & 22 and flexible dosing 25-50 mg biweekly starting from day 36 Duration: 53-weeks	Reduced symptoms • Risperidone > Paliperidone	Adverse effect rate • Risperidone = paliperidone Insomnia (most frequent adverse event) • Risperidone = Paliperidone
Fu et al, 2014[297] Subgroup analysis of a 13- week, randomized, double-blind, double-dummy, parallel-group, multicenter comparative trial[299]	292	Markedly-to-severely ill schizophrenia patients	Paliperidone palmitate 234 mg day 1 and 156 mg day 8 Followed by once-monthly flexible dosing + matched risperidone placebo Risperidone long-acting injection 25 mg, days 8 and 22; followed by biweekly flexible dosing + matched paliperidone placebo Duration: 13-weeks	Reduced symptoms • Paliperidone = Risperidone > Baseline, $p < 0.05$ •	Headache • Paliperidone: 6.3% • Risperidone: 14.0% Somnolence • Paliperidone: 7.8% • Risperidone: 1.3% Akathisia • Paliperidone: 7.0 % • Risperidone: 5.3% Injection site reaction • Paliperidone: 5.6% • Risperidone: 1.3%

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Fu et al, 2014[300] Double-blind, double-dummy, multicenter Trial	334	Patients recently diagnosed with schizophrenia (≤ 5 years)	Paliperidone palmitate once-monthly flexible-dose (n=161; 234 mg day 1 and 156 mg day 8) Risperidone long-acting injection biweekly flexible-dose RLAI (n=173) Duration: 13 weeks	Reduced symptoms • Paliperidone = Risperidone	Overall adverse event rates • Paliperidone: 54.7% • Risperidone: 50.3%, Extrapyramidal effects • Paliperidone: 11.2% • Risperidone: 8.1% Increased prolactin levels • Paliperidone: 2.5% • Risperidone: 2.3%
Gaebel et al, 2010[296] Open-label, randomized, active-controlled trial	710	Patients with schizophrenia or related disorders on stable treatment with oral risperidone, olanzapine or first-generation antipsychotic agents	All patients switched to: Risperidone long-acting injection (n = 329) Quetiapine, oral (n = 337)	Time to relapse • Risperidone > Quetiapine, p = 0.0001 Relapse rate • Risperidone: 16.5% • Quetiapine: 31.3%	Weight gain • Risperidone: 7% • Quetiapine: 6% Extrapyramidal effects • Risperidone: 10% • Quetiapine: 6% Hyperprolactinemia • Risperidone: 13.1% • Quetiapine: 1.5% Somnolence • Risperidone: 2% • Quetiapine: 11%
Harvey et al, 2013[306] 6 month, double-blind extension trial	267	Patients with Schizophrenia	Lurasidone 40-160 mg daily Quetiapine ER 200-800 mg daily Placebo Duration: 6 months	Cognitive performance and functional Capacity <u>6 weeks</u> • Lurasidone 160 mg > Quetiapine = Placebo <u>6 months</u> • Lurasidone > Quetiapine	Not reported

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Jin et al, 2013[288] Open-label, flexible dosing, randomized, controlled trial	332	Patients, aged >40 years, with psychosis associated with schizophrenia, mood disorders, PTSD, or dementia	Aripiprazole Olanzapine Quetiapine Risperidone Duration: up to 2 years	Treatment discontinuation rate • Aripiprazole:81.5% • Olanzapine: 79-81% • Quetiapine: 78.6% • Risperidone: 79-81%	Serious adverse events* • Quetiapine > all other agents, p = 0.002 *Quetiapine arm of trial was discontinued Non-serious adverse events • Aripiprazole: 49% • Quetiapine: 78%, p = 0.03 • Risperidone: 46% • Olanzapine: 73%, p = 0.04 Metabolic syndrome (at one year) • Aripiprazole: 86% • Olanzapine: 55%, p = 0.013
Li et al, 2011[298] Open-label, rater-blinded, parallel-group trial	452	Patients with acute schizophrenia	Paliperidone palmitate monthly injection (n = 229) Risperidone long-acting biweekly injection (n = 223) Duration: 13-weeks	Reduced symptoms • Paliperidone = Risperidone	Treatment emergent adverse events • Paliperidone = Risperidone
Li et al, 2013[102] Open-label, switch trial	213	Patients with schizophrenia and metabolic disorders switched from clozapine to ziprasidone	Clozapine => Ziprasidone Duration= 24-weeks	Reduced symptoms • Ziprasidone >Clozapine, $p < 0.05$	Metabolic effects (BMI, cholesterol) • Ziprasidone < Clozapine, $p < 0.05$

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Li et al, 2014[293] Randomized, double-blind, active parallel-controlled, multicenter clinical trial	279	Patients with primary diagnosis of schizophrenia	Aripiprazole (n = 139) Risperidone (n = 140) Duration: 6-weeks	Reduced symptoms • Aripiprazole = Risperidone	Extrapyramidal effects: • Aripiprazole = Risperidone Weight gain • Risperidone > Aripiprazole, p = 0.0118 Hyperprolactinemia • Risperdal > Aripiprazole, p = 0.001
Loebel et al, 2013[305] Randomized, double-blind, placebo- and active-controlled trial	486	Recently admitted inpatients with schizophrenia with an acute exacerbation of psychotic symptoms	Lurasidone 80 mg daily (n = 125) Lurasidone 160 mg daily (n = 121) Quetiapine XR 600 mg daily (n = 119) Placebo (n = 121) Duration: 6-weeks	Reduced symptoms • Lurasidone = Quetiapine	Weight gain • Lurasidone: 4% • Quetiapine: 15%, p = NS
Loebel et al, 2013[304] Double-blind, noninferiority study	488	Outpatients with an acute exacerbation of chronic schizophrenia	Lurasidone 40-160 mg daily Quetiapine 200-800 mg daily Duration: 12 months	Relapse rate • Lurasidone = Quetiapine Remission rate • Lurasidone > Quetiapine, p = 0.043 Hospital readmission rate • Lurasidone < Quetiapine, p = 0.049	Discontinuation adverse event rate • Lurasidone: 7% • Quetiapine: 5%

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Olivares et al, 2009[295] Prospective, observational study	1622	Patients with schizophrenia	Risperidone long-acting injection (n = 1345) New oral antipsychotic agent (n = 277; 35.7% risperidone and 36.5% olanzapine) Duration: up to 2 years	Treatment retention at 24-months • Injectable risperidone: 81.8% • Oral agents: 63.4%, p < 0.0001 Reduction of symptoms • Risperidone > Oral agents, p = 0.0165 Reduced hospitalization • Risperidone > Oral agents, p < 0.01	Not reported
Pandina et al, 2011[299] Double-blind, non-inferiority trial	1220	Adult patients with schizophrenia	Paliperidone palmitate (n = 610) Risperidone long-acting injectable (n = 610) Duration: 13-weeks	Reduced Symptoms • Paliperidone = Risperidone	Injection site pain • Risperidone < Paliperidone Anxiety • Risperidone < Paliperidone Constipation • Paliperidone < Risperidone Insomnia • Risperidone < Paliperidone
Potkin et al, 2011[311] Randomized, double-blind, fixed-dose controlled trial	301	Adult outpatients who met DSM-IV criteria for schizophrenia or schizoaffective disorder	Lurasidone 120 mg once daily (n=150) Ziprasidone 80 mg twice daily (n=151) Duration: 21-days	Efficacy discontinuation rate • Lurasidone = Ziprasidone Reduced symptoms • Lurasidone = Ziprasidone	Adverse effect discontinuation rate • Lurasidone = Ziprasidone

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Potkin et al, 2013[303] Pooled analysis of two 26-week core studies and extensions	502	Patients with Schizophrenia	Asenapine 5-10 mg twice daily Olanzapine 5-20 mg once daily Duration: 52-weeks	Reduced symptoms @ 52 weeks • Asenapine > Olanzapine	Treatment-related adverse event rate • Asenapine > Olanzapine
Sanz-Fuentenebro et al, 2013[294] Randomized, open-label, multi-center controlled trial	30	Treatment-naïve patients with first-episode schizophrenia	Clozapine Risperidone Duration: one year	Reduced symptoms • Clozapine = Risperidone Adherence rates • Clozapine > Risperidone	Metabolic effects • Clozapine = Risperidone > Baseline
Schnell et al, 2014[310] Randomized, controlled trial	30	Patients with schizophrenia and cannabis abuse/ dependence	Clozapine Ziprasidone Duration: 12 months	Reduced symptoms • Clozapine > Ziprasidone Adherence rate • Ziprasidone > Clozapine Cannabis use • Clozapine = Ziprasidone < Baseline	Adverse effect rate • Clozapine > Ziprasidone
Schreiner et al, 2015[289] Randomized, rater-blinded controlled trial	764	Patients with a recent diagnosis of schizophrenia	Paliperidone Palmitate injection (n = 376) Oral antipsychotic (n = 388) Aripiprazole (n = 81) Haloperidol (n = 34) Olanzapine (n = 49) Paliperidone ER (n = 77) Quetiapine (n = 65) Risperidone (n = 57) Duration: up to 24-months	Reduced symptoms • Paliperidone = Oral agents Time to relapse • Paliperidone > Oral agents, p = 0.019	Adverse event rate • Paliperidone = Oral agents

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Sevy et al, 2011[290] Randomized, controlled trial	49	First-episode schizophrenia patients with cannabis use disorders	Olanzapine (n = 28) Risperidone (n = 21) Duration: 16-weeks	Reduced symptoms • Olanzapine = Risperidone Cannabis use • Olanzapine = Risperidone	Weight gain • Olanzapine = Risperidone > Baseline
Walther et al , 2014[291] Prospective, randomized, rater-blinded, controlled trial	43	Severely agitated patients with schizophrenia at acute care psychiatric units	Haloperidol 15 mg daily Olanzapine 20 mg daily Risperidone 2-6 mg daily Duration: 5 days	Rapid Tranquilization* • Olanzapine = Risperidone *increased efficacy demonstrated in men compared to women	Adverse event rate • Olanzapine = Risperidone
Tourette's disorder					
Ghanizadeh et al, 2013[327] Randomized, double-blind clinical trial	60	Children and adolescents with tic disorder	Aripiprazole Risperidone Duration: 2 months	Reduced symptoms • Aripiprazole = Risperidone > Baseline Quality of life • Aripiprazole = Risperidone > Baseline Social functioning • Risperidone > Aripiprazole	Adverse event rate • Aripiprazole = Risperidone

Key: NS = not significant

Evidence Table 3. Placebo Controlled Evidence for the Newest Antipsychotic Agents

Reference	Abstract
Correll et al, 2015[66]	"OBJECTIVE: The efficacy, safety, and tolerability of brexpiprazole and placebo were compared in adults with acute schizophrenia. METHOD: This was a multicenter, randomized, double-blind, placebo-controlled study. Patients with schizophrenia experiencing an acute exacerbation were randomly assigned to daily brexpiprazole at a dosage of 0.25, 2, or 4 mg or placebo (1:2:2:2) for 6 weeks. Outcomes included change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total score (primary endpoint measure), Clinical Global Impressions Scale (CGI) severity score (key secondary endpoint measure), and other efficacy and tolerability measures. RESULTS: The baseline overall mean PANSS total score was 95.2, and the CGI severity score was 4.9. Study completion rates were 62.2%, 68.1%, and 67.2% for patients in the 0.25-, 2-, and 4-mg brexpiprazole groups, respectively, versus 59.2% in the placebo group. At week 6, compared with placebo, brexpiprazole dosages of 2 and 4 mg produced statistically significantly greater reductions in PANSS total score (treatment differences: -8.72 and -7.64, respectively) and CGI severity score (treatment differences: -0.33 and -0.38). The most common treatment-emergent adverse event for brexpiprazole was akathisia (2 mg: 4.4%; 4 mg: 7.2%; placebo: 2.2%). Weight gain with brexpiprazole was moderate (1.45 and 1.28 kg for 2 and 4 mg, respectively, versus 0.42 kg for placebo at week 6). There were no clinically or statistically significant changes from baseline in lipid and glucose levels and extrapyramidal symptom ratings. CONCLUSIONS: Brexpiprazole at dosages of 2 and 4 mg/day demonstrated statistically significant efficacy compared with placebo and good tolerability for patients with an acute schizophrenia exacerbation."
Sachs et al, 2015[70]	"BACKGROUND: This Phase III, randomized, double-blind, placebo-controlled study investigated the efficacy and tolerability of flexibly-dosed cariprazine in patients with acute manic or mixed episodes associated with bipolar I disorder. METHODS: Patients were randomized to 3 weeks of double-blind treatment with cariprazine 3-12mg/day (n=158) or placebo (n=154). The primary efficacy parameter was change from baseline to Week 3 in Young Mania Rating Scale (YMRS) total score. The secondary efficacy parameter was change from baseline to Week 3 in Clinical Global Impressions-Severity (CGI-S) score. RESULTS: Mean change from baseline to Week 3 in YMRS total score was significantly greater for patients receiving cariprazine 3-12mg/day versus placebo (P=0.0004). Significant differences between groups in YMRS total score mean change were observed by Day 4 (first postbaseline assessment) and maintained throughout double-blind treatment (all assessments, P<0.01). Cariprazine also demonstrated statistically significant superiority over placebo on YMRS response (≥50% improvement: cariprazine, 58.9%; placebo, 44.1%; P=0.0097) and remission (YMRS total score≤12: cariprazine, 51.9%; placebo, 34.9%; P=0.0025) and mean change in CGI-S (P=0.0027) score and Positive and Negative Syndrome Scale (PANSS) (P=0.0035) total score. The most common cariprazine-related (≥10% and twice placebo) treatment emergent adverse events (TEAEs) were akathisia, extrapyramidal disorder, tremor, dyspepsia, and vomiting. Mean change from baseline in metabolic parameters were generally small and similar between groups. LIMITATIONS: Lack of active comparator arm; short duration of study.

	CONCLUSION: In this study, cariprazine 3-12mg/day was effective and generally well tolerated in the treatment of manic and mixed episodes associated with bipolar I disorder."
Durgam et al, 2014[76]	"INTRODUCTION: Cariprazine is an orally active and potent D3 and D2 partial agonist with preferential binding to D3 receptors in development for the treatment of schizophrenia and bipolar mania. This study (NCT00694707) evaluated the efficacy and safety of cariprazine in patients with acute exacerbation of schizophrenia. METHODS: This study was a multinational, double-blind, randomized, placebo- and active-controlled, fixed-dose trial. Patients were randomized to receive placebo, cariprazine 1.5mg/d, cariprazine 3.0mg/d, cariprazine 4.5mg/d, or risperidone 4.0mg/d (for assay sensitivity) for 6 weeks of double-blind treatment and 2 weeks of safety follow-up. Primary and secondary efficacy parameters were change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) total and Global Impressions-Severity of Illness (CGI-S) scores, respectively. Safety parameters included adverse events (AEs), vital signs, laboratory measures, and extrapyramidal symptom (EPS) scales. RESULTS: Of 732 randomized patients, 64% completed the study. PANSS total score improvement at Week 6 was statistically significant versus placebo for cariprazine 1.5mg/d, 3.0mg/d, and 4.5mg/d (least squares mean difference [LSMD]: -7.6, -8.8, -10.4, respectively; $p<0.001$; LOCF) and risperidone (-15.1, $p<0.001$; LOCF); significant improvement on CGI-S was demonstrated for all active treatments ($p<0.05$). The most frequent cariprazine AEs (≥ 5% and at least twice the rate of the placebo group) were insomnia, extrapyramidal disorder, akathisia, sedation, nausea, dizziness, and constipation. Mean changes in metabolic parameters were small and similar between groups. CONCLUSION: The results of this study support the efficacy and safety of cariprazine in patients with acute exacerbation of schizophrenia."
Calabrese et al, 2015[214]	"OBJECTIVE: This phase 3 trial evaluated the efficacy, safety, and tolerability of low- and high-dose cariprazine in patients meeting DSM-IV-TR criteria for acute manic or mixed episodes associated with bipolar I disorder. METHOD: This multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed/flexible-dose study was conducted from February 2010 to December 2011. Patients were randomly assigned to placebo, cariprazine 3-6 mg/d, or cariprazine 6-12 mg/d for 3 weeks of double-blind treatment. Primary and secondary efficacy parameters were change from baseline to week 3 in Young Mania Rating Scale (YMRS) total score and Clinical Global Impressions-Severity of Illness (CGI-S) score, respectively. Post hoc analysis examined change from baseline to week 3 in YMRS single items. RESULTS: A total of 497 patients were randomized; 74% completed the study. The least squares mean difference (LSMD) for change from baseline to week 3 in YMRS total score was statistically significant in favor of both cariprazine groups versus placebo (LSMD [95% CI]: 3-6 mg/d, -6.1 [-8.4 to -3.8]; 6-12 mg/d, -5.9 [-8.2, -3.6]; $P < .001$ [both]). Both cariprazine treatment groups showed statistically significant superiority to placebo on all 11 YMRS single items (all comparisons, $P < .05$). Change from baseline in CGI-S scores was statistically significantly greater in both cariprazine groups compared with placebo (LSMD [95% CI]: 3-6 mg/d, -0.6 [-0.9 to -0.4]; 6-12

	mg/d, -0.6 [-0.9 to -0.3]; P < .001 [both]). The most common (≥ 5% and twice the rate of placebo) treatment-related adverse events for cariprazine were akathisia (both groups) and nausea, constipation, and tremor (6-12 mg/d only). CONCLUSIONS: Results of this study demonstrated that both low- and high-dose cariprazine were more effective than placebo in the treatment of acute manic or mixed episodes associated with bipolar I disorder. Cariprazine was generally well tolerated, although the incidence of akathisia was greater with cariprazine than with placebo."
Kane et al, 2015[212]	"The objective of this study was to evaluate the efficacy, safety and tolerability of brexpiprazole versus placebo in adults with acute schizophrenia. This was a 6-week, multicenter, placebo-controlled double-blind phase 3 study. Patients with acute schizophrenia were randomized to brexpiprazole 1, 2 or 4 mg, or placebo (2:3:3:3) once daily. The primary endpoint was changed from baseline at week 6 in Positive and Negative Syndrome Scale (PANSS) total score; the key secondary endpoint was Clinical Global Impressions-Severity (CGI-S) at week 6. Brexpiprazole 4 mg showed statistically significant improvement versus placebo (treatment difference: -6.47, p=0.0022) for the primary endpoint. Improvement compared with placebo was also seen for the key secondary endpoint (treatment difference: -0.38, p=0.0015), and on multiple secondary efficacy outcomes. Brexpiprazole 1 and 2mg also showed numerical improvements versus placebo, although p>0.05. The most common treatment-emergent adverse events were headache, insomnia and agitation; incidences of akathisia were lower in the brexpiprazole treatment groups (4.2%-6.5%) versus placebo (7.1%). Brexpiprazole treatment was associated with moderate weight gain at week 6 (1.23-1.89 kg versus 0.35 kg for placebo); there were no clinically relevant changes in laboratory parameters and vital signs. In conclusion, brexpiprazole 4 mg is an efficacious and well-tolerated treatment for acute schizophrenia in adults."
Thase et al, 2015[65]	"OBJECTIVE: To evaluate efficacy, safety, and tolerability of brexpiprazole adjunctive to antidepressant treatments (ADTs) in patients with major depressive disorder (as defined by DSM-IV-TR criteria) with inadequate response to ADTs. METHOD: Patients still depressed despite 1-3 prior ADTs followed by 8 weeks of prospective physician-determined, open-label ADT were randomized (1:1:1) to double-blind brexpiprazole 3 mg/d, brexpiprazole 1 mg/d, or placebo for 6 weeks. The primary efficacy end point was change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to week 6. The key secondary efficacy end point was change in Sheehan Disability Scale mean score. The Hochberg procedure corrected for multiplicity. The efficacy population comprised all patients who had ≥ 1 dose of study drug with baseline and ≥ 1 postrandomization MADRS scores; the efficacy population per final protocol consisted of efficacy population patients meeting amended criteria for inadequate response throughout the 8-week prospective ADT. The study was conducted between June 2011 and September 2013. RESULTS: In the efficacy population per final protocol, brexpiprazole 3 mg (n = 213) showed a greater improvement in MADRS total score versus placebo (n = 203; -8.29 vs -6.33; P = .0079), whereas brexpiprazole 1 mg did not (n = 211; -7.64 vs -6.33; P = .0737). The brexpiprazole groups showed comparable improvement in SDS mean score versus placebo (least squares [LS] mean difference: [1 mg] -0.49, P = .0158; [3 mg] -0.48, P = .0191). The most frequent adverse events were akathisia (4.4%, 13.5%, 2.3%), headache (9.3%, 6.1%, 7.7%), and weight increase (6.6%, 5.7%, 0.9%) in brexpiprazole 1-mg, 3-mg, and placebo groups, respectively. Mean changes from baseline in Abnormal Involuntary Movement Scale (LS mean difference = 0.08, P = .0141) and Barnes Akathisia Rating Scale (LS mean difference = 0.17, P = .0001) total scores were significantly greater with brexpiprazole 3 mg versus placebo. CONCLUSIONS:

	Brexpiprazole 3 mg demonstrated efficacy versus placebo in the efficacy population per final protocol. Both doses of brexpiprazole were well tolerated."
Thase et al, 2015[64]	"OBJECTIVE: To assess the efficacy, tolerability, and safety of brexpiprazole as adjunctive therapy to antidepressant treatments (ADTs) in adults with major depressive disorder (as defined by DSM-IV-TR criteria) and inadequate response to ADTs. METHOD: Patients with historical inadequate response to 1-3 ADTs were enrolled. All patients entered a prospective 8-week phase on physician-determined, open-label ADT. Those with inadequate response were randomized to ADT + brexpiprazole 2 mg/d or ADT + placebo for 6 weeks. The study was conducted between July 2011 and May 2013. The primary efficacy end point was change from baseline to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total score. The key secondary end point was change from baseline to week 6 in Sheehan Disability Scale (SDS) mean score. The efficacy population comprised all patients who had ≥ 1 dose of study drug in the double-blind phase and both baseline and ≥ 1 postrandomization MADRS scores. The efficacy population per final protocol included patients from the efficacy population who met amended randomization criteria of inadequate response throughout prospective treatment. RESULTS: Brexpiprazole (n = 175) reduced mean MADRS total score versus placebo (n = 178) at week 6 in the efficacy population per final protocol (-8.36 vs -5.15, P = .0002). Brexpiprazole improved SDS mean score versus placebo (-1.35 vs -0.89, P = .0349). The most common treatment-related adverse events were weight gain (brexpiprazole, 8.0%; placebo, 3.1%) and akathisia (7.4% vs 1.0%). CONCLUSIONS: Adjunctive brexpiprazole therapy demonstrated efficacy and was well tolerated in patients with major depressive disorder and inadequate response to ADTs."